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OF
PROGRAM ACTIVITIES

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1962

DIVISION OF BIOLOGICS STANDARDS
DIVISION OF GENERAL MEDICAL SCIENCES
DIVISION OF RESEARCH FACILITIES AND RESOURCES
DIVISION OF RESEARCH GRANTS
DIVISION OF RESEARCH SERVICES

NATIONAL INSTITUTES OF HEALTH
PUBLIC HEALTH SERVICE
U. S DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

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ANNUAL REPORT OF PROGRAM ACTIVITIES

Division of Biologics Standards

January - December 1962

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ANNUAL REPORT

DIVISION OF BIOLOGICS STANDARDS

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DIVISION OF BIOLOGICS STANDARDS

INTRODUCTION

The Division of Biologics Standards, which has the responsibility for administering the provisions of the Public Health Service Act with respect to the control of biological products, discharges this task as a blend of research and administrative activities which are about equally divided between control and research. The research programs are concerned largely with the basic function of the Division -- the control of biological products -- although by their very nature, some of these activities could well be classified as basic or fundamental research. However, no programs are undertaken initially unless they have direct bearing on the responsibilities of the Division. The activities of the Division -- both control and research -- are therefore product-oriented, and their scope, direction, and intensity are dictated by the need to provide essential information for developing requirements and regulations for the licensing and release of biological products. The Division research program is vital in this respect.

It is characteristic of the type of responsibility which the Division has, with its ultimate objective the protection of the public against unsafe and uneffective biological products, that the Division is confronted with a series of problems which are often never completely solvable. The successful accomplishments of the Division reside in those instances where difficulties are anticipated, headed off, or abated. It is necessary to maintain an active scientific interest in products which have long since been routinely accepted by the medical and health professions, and in some instances even forgotten by the majority of scientists working within the field. The Division can never move its area of interest completely or abandon a concern for any of the products which remain licensed. Smallpox vaccine is an excellent example.

During 1962, the Division faced problems similar in pattern to those encountered in 1961. Live poliovirus vaccine, types 1 and 2, were licensed in 1961, but the problems encountered with type 3 and which delayed its licensing were carried over into 1962. The type 3 strain is genetically the most unstable, and the major difficulties concerned the consistent production of consecutive lots of vaccine which would meet the requirements for a low degree of neurovirulence in monkeys as well as the specific marker characterizations required in tissue culture. The availability of only two of the required three types of live poliovirus vaccine severely limited the large scale immunization programs which had been visualized by health authorities and local medical groups. However, many of these programs were started in anticipation of the eventual licensing of the type 3 vaccine which took place on March 27, 1962. During the latter part of 1962 the safety of the type 3 vaccine was called into question by the occurrence of a few cases of poliomyelitis in association with the administration of type 3 vaccine. This situation which was examined thoroughly over a period of some months by the Public Health Service and its advisors was finally resolved with the report by the Surgeon General in December 1962, which in effect stated that there was a minute hazard but that this appeared to be confined to persons over 30 years of age. This period of time was a difficult one for the Division. Even though the main type 3 problem has now been solved, the control of this vaccine calls for special vigilence.

The monkey neurovirulence tests required for all three types of live poliovirus vaccines involved extensive studies. More than 150 neurovirulence tests have been made in more than 4,000 monkeys since the first vaccine samples were submitted to the Division for testing by the manufacturers. This testing has provided a wealth of information and experience that is invaluable in judging the validity of individual tests.

Research, testing, and the development of standards in connection with measles vaccine was a second item of major concern during 1962, and by the end of the year, most of the necessary work had been completed to the point that the general availability of measles vaccine as a licensed product appeared to be only weeks or months off.

In the development of requirements for measles vaccine, the Division has drawn on its experience with other vaccines grown in tissue culture, the most comprehensive of which was with the poliomyelitis vaccines. However, since each virus has its own characteristics, and the properties of live vaccines depend on such factors as how the vaccine virus enters the body, where it proliferates, and what elements -- mechanical, physiological, immunological, and virological -- favor or inhibit its ability to "take," one vaccine is not truly comparable to another.

The requirements cover the characteristics of the measles virus strains to be used in the vaccine; the exclusion of adventitious agents from the virus fluid used in manufacture; the employment of a variety of animal and tissue culture test methods; the demonstration of satisfactory clinical use of the vaccine, including clinical effectiveness; and the stability of the live virus vaccine strains in terms of capacity to revert to significant virulence for man.

As with all new biological products, the information most difficult to obtain concerns the stability of the product under conditions of actual use, yet without this information a realistic dating period cannot be set. In this regard field studies such as those conducted in Upper Volta are of great value.

An important need in the testing of measles vaccine is a supply of monkeys that are susceptible to measles virus. While monkeys are susceptible to measles infection, they are not exposed to it under natural conditions. However, during procurement and shipping, they readily develop an imperceptible measles infection on contact with infected monkeys or human beings. As a result, almost all of the animals have developed resistance to measles infection by the time they reach the laboratory. This renders them unsuitable for many of the tests required in the evaluation of the vaccine. Therefore, special procurement, handling, and transportation of these animals are essential, as well as special quarantine and conditioning requirements prior to and during their use in measles vaccine studies.

A difficult problem encountered in working with tissue culture produced vaccines is the occurrence of adventitious viruses, many of them previously unknown. Their presence in the tissue cultures used for production of viruses represents a complicating factor in production and testing procedures. Since their role in the cause of human disease is rarely demonstrable, the only course

to pursue is to exclude them from the final product insofar as is possible with available testing methods.

Experience with the simian virus, SV-40, sharply emphasized the problem of viruses that are unidentifiable by tests normally employed. Although no relationship of SV-40 to the development of human disease has been demonstrated, this virus is associated with the production of tumors when inoculated into baby hamsters and, under certain conditions, tissue cultures infected with the virus show changes that suggest a tumor-producing potential. In order to insure that this adventitious agent would be excluded from commercial vaccines, new methodology was developed and adequate test procedures were designed as a result of extensive research conducted by members of the Division staff.

The production of measles virus in chick embryo tissue culture also presents a problem since a number of adventitious agents are known to be present in fowls. Although vaccine produced in the developing embryo of the hen's egg is well tolerated by human beings as demonstrated by the large-scale use of yellow fever, typhus, and influenza vaccines for more than 20 years, analogous experience with chick embryo tissue culture is limited.

One approach towards the resolution of some of the testing problems encountered with adventitious viruses is the development of continuous cell line tissue culture preparations which would obviate the use of primary cell cultures. Such a cell line has been initiated by the Division using kidney tissue of the African green monkey. The cell line is now at a high passage level and its continuous growth is considered to be established. These cells have not changed their sensitivity to SV-40 virus, and are sensitive to attenuated measles virus as well as a variety of other viruses. Continuous cell lines while useful for test purposes are not used at the present time for the production of virus harvests to be used in the actual manufacture of virus vaccines. The recent report of an NIH Committee on Tissue Culture Virus and Vaccines on this subject should clarify the direction of future research toward this end. (Science 1963, 139, 15-20)

During the past year a number of variants of the influenza virus strains have appeared in this country. In cooperation with other interested laboratories, the Division has paid close attention to these variants with a view to the possible selection of an additional virus strain for inclusion in the vaccine now in use. The last change was in 1957 when the Asian strain of influenza virus spread throughout the world. By December 1962, it appeared that the incorporation of new strains in the vaccine would again be called for and appropriate studies were initiated by the Division in cooperation with manufacturers and specialists in this field.

Industry continues to attempt to meet the demand by the medical profession for multiple antigens that will immunize against several diseases simultaneously, although the preparation of these products is a complex process. This is especially true of the so called quadruple antigen vaccine which is used in pediatric practice. This product is composed of diphtheria and tetanus toxoids combined with pertussis and poliomyelitis vaccines. Studies conducted by the Division on the stability of this product revealed that there was a significant decrease in the potency of the pertussis component during the prescribed dating period. The reasons for this are obscure. However, as a

result of the investigations, the dating period for this product was shortened and the potency requirement of the pertussis component increased in order to ensure that the potency of the pertussis component does not fall below the required minimum level even when the product is exposed to variable market conditions. Manufacturers are attempting to meet this problem by bypassing it. Double chambered syringes and dual packaging of the components are being offered.

The shortage of adequate laboratory and animal space continues to be acute for all activities within the Division. It is not anticipated that this will improve until the new facilities now in the planning stage are occupied, although the remodeling of animal quarters which have become available in Building 14 should help somewhat when this job is completed during the latter part of 1963.

A great deal of time and effort has been expended during 1962 in the investigation connected with alleged violations of the Biologic Law in the sale of plasma and whole blood. These investigations, carried out under direction of the U. S. Department of Justice continued to consume the time and resources of the Division's Laboratory of Blood and Blood Products. It is anticipated that these cases will come to trial early in 1963.

The recruitment of suitable personnel, particularly senior scientists willing to engage in the type of scientific work presented by the Division and willing to accept the kind of responsibilities involved, continues. The anticipated retirement of a number of senior staff members in 1963 will present additional difficulties in this respect.

The following summaries of the programs of each of the laboratories present more details of the activities of the Division

LABORATORY OF CONTROL ACTIVITIES

This Laboratory is responsible for activities dealing directly with licensed establishments in relation to the licensing and control of biological products. It is supported by sections on control tests, pyrogens, and reference standards.

Its activities include:

(a) Determination of eligibility of establishments and of individual biological products for license. This determination is made on the basis of the integrity of management and technical personnel, the physicial facilities for manufacturing and testing of products, the scientific and professional qualifications of personnel and the evidence developed by manufacturers and the Division of continued safety, purity, and potency of products, for which an application for license is being evaluated. License applications are reviewed individually when required by an ad hoc committee consisting of appropriate members of the staff of the Division.

(b) Supervision of annual and special inspections of licensed establishments and of those for which an application for license has been made.

(c) Releasing of individual lots of biological products for distribution by manufacturers on the basis of review of manufacturers' and of DBS tests and of any other available information relating to the safety, purity, and potency of the lot of the product.

(d) The establishment and distribution of physical biological standards, reference preparations, and control materials. A small culture collection is also maintained mainly for the Division and for licensed manufacturers.

(e) Review of requirements and regulations now in effect for such constructive revision as needed and the development of requirements and regulations for new products.

(f) Maintenance of close working relations with other laboratories of the Division and other agencies to insure continuous knowledge of information needed for the licensing of establishments and new products and for the testing, release, and control of products already licensed.

The scope of activities carried out by this Laboratory is indicated by the fact that during the twelve month period, December 1, 1961 - November 30, 1962, a total of 7,007 control tests were carried out to insure the sterility, safety, potency, and purity of licensed biological products as follows:

Products for Release	6,103	Tests
Inspection Samples	886	"
Complaint Investigations	18	"
Total	7,007	

These results served as a basis for the release or rejection of individual lots of products. In addition, 1,193 cooperative service tests were done on biological products not licensed.

During the same period 5,041 lots of biological products were submitted for release by licensed manufacturers. Of these 4,915 lots were released, 56 lots rejected, and 70 lots withdrawn from consideration for release by manufacturers.

To maintain an adequate supply of physical reference standards for use by the licensed manufacturers in their official control testing, it is necessary to prepare and standardize new liquid lots from the primary dried stocks. The number of lots prepared and standardized during the year were: antitoxins - 19, serums - 5, vaccines - 1, toxoids - 3, and toxins - 3. A total of 701 tests were required to complete a satisfactory standardization of these lots. These tests include flocculation reactions, animal protection tests, animal potency tests, and a number of specialized tests for specific products.

Standards, reference preparations, and cultures are freeze-dried for greater stability during storage. The following were dried between November 15, 1961, and November 15, 1962:

Cultures	1,340	Ampules
Serums	1,407	"
Vaccines	1,837	"
Viruses	2,630	"
Toxins	2,146	"
Total	9,960	

Official standards, reference, and control preparations currently maintained include 75 items.

Standards, reference preparations, and cultures were distributed to research or control laboratories of licensed and other manufacturers, health departments, and universities in this country and abroad as follows:

Antitoxins	500
Serums	1,861
Vaccines	883
Toxins	356
Bacterial & Viral Cultures	2,271

LABORATORY OF BACTERIAL PRODUCTS

During 1962 the Laboratory was able to increase its research activities with the addition of scientific personnel. With the available space being used to capacity with 2--4 persons per room, an expansion of the program to cover bacterial products which need investigation must be curtailed until more space is available. Two student candidates for Ph. D. degrees have strengthened the staff.

Allergenic Products. Dr. Harold Baer and his associates have made considerable progress in their studies on tuberculin and poison ivy extracts. Both carbohydrate and protein fractions which have been separated from tuberculin elicit skin reactions in sensitized guinea pigs. The carbohydrate fraction shows a greater specificity in homologously sensitized guinea pigs than those sensitized with mycobacteria of other species.

The skin reactivity of poison ivy extract and pentadecylcatechol, a reactive component, on sensitized guinea pigs has been shown to be directly related to the amount of the catechols as measured by gas chromatography. If these results are successfully correlated with human reactivity, tests of which are anticipated in the immediate future, sufficient information will be available for the establishment of a U. S. Standard of Potency for poison ivy extracts and the designation of a standard reference preparation. Fundamental information on sensitization and blocking of sensitization is being obtained.

The liason activities with the Committee on Standardization of Allergens (NIAID) of which Dr. Baer is a member continue. It is anticipated that current work of investigators on ragweed pollen will furnish basic information that will be applicable to the establishment of standards for ragweed products.

Bacterial Toxins. The addition of Dr. M. Carolyn Hardegree to the staff has strengthened the work on tetanus toxoids. The experimental work on potency assay of toxoids and the correlation on laboratory measured potency with field response in pregnant native women in the Territory of Papua and New Guinea for the prevention of neonatorum tetanus is well underway. A project has been initiated on the study of the toxins of Clostridium tetani.

The work on the Schick Test Toxin (Diphtheria) and the revisions of the requirements for this product should be completed early in 1963.

Much of Dr. Michael Barile's work is devoted to the study of pleuropneumonia-like organisms. He has formulated the test to be used for the detection of the presence of PPLO in measles virus vaccine and is currently engaged in screening lots of the vaccine submitted in support of license applications. He cooperated in a study with NIAID in which the Eaton agent was shown to be a PPLO.

Bacterial Vaccines. The cooperative study with the World Health Organization on typhoid vaccine is proving to be very profitable. It has been found that the route of vaccination of the mouse significantly affects the measured relative potency between the field trial vaccines which are prepared by different methods. The acetone-killed-dried vaccine in the field has given excellent protection which is three or more times better than that obtained with the heat-killed-phenolized vaccine. Only by the intraperitoneal route of vaccination has this relation been shown by us in animal tests. The final evaluation of the WHO project will be very valuable in prescribing methods for the preparation and control of typhoid vaccine.

An investigation on the cause of instability of pertussis vaccine in the presence of poliomyelitis vaccine has been initiated. The temporary removal of the quadruple antigen product from the market curtailed the investigation on the adequacy of the revised specifications for the product.

The revision in the toxicity test for pertussis vaccine has resulted in products of lower mouse reactivity without an apparent decrease in potency. The preliminary study with Dr. J. A. Bell indicates that there is a possible relationship between mouse toxicity and reactivity in children. More information is greatly needed.

In the studies on cholera it has been shown that cholera vaccine in the mouse is as protective against the El Tor strains as against classic cholera strains. A revision of the requirements for cholera vaccine in which the newly developed potency test will be included is in preparation. The conditions whereby the hemolytic activity of El Tor vibrios can be uniformly determined have been defined by Dr. J. C. Feeley. The test should be helpful in epidemiological studies of cholera. His recent paper on methods of cultural isolation of cholera vibrios should, also, be helpful.

Results of the sterility test study by Mrs. Claire B. Cox suggest that Fluid Thioglycollate Medium is better for promotion of growth of fungi than the presently required Fluid Saboraud's Medium but the use of two temperatures of incubation remains essential.

Non-research activities. During the year, 571 tests were performed relating to the control of pertussis vaccine, antipertussis serum and Haemophilus influenzae therapeutic and diagnostic sera.

Other regulatory activities consisted in (1) the formulation of revised standards for pertussis vaccine and (2) participation in the review of license applications to determine eligibility for establishments and of individual products for licenses, inspection of establishments and liason activities between the Division and one manufacturer of pertussis vaccine.

A reevaluation of the potency of the U. S. Standard Pertussis Vaccine Lot No. 6 was made and a number of courtesy pertussis-vaccine potency tests were made for reference preparations of national control laboratories and for WHO to determine if the International Standard for pertussis vaccine was stable.

LABORATORY OF VIRAL IMMUNOLOGY

Work with the oral, live poliovirus vaccine has continued at an accelerated pace during the past year. Not only did new production laboratories make their appearance, but work with the type 3 virus was expanding. When the data had been received and analyzed, new licenses were issued to Pfizer, Ltd. of Sandwich, England for type 3 Poliovirus Vaccine, to Lederle Laboratories, Pearl River, New York for type 1, type 2, and type 3 Poliovirus Vaccines and to Wyeth Laboratories, Marietta, Pennsylvania, for type 1 and type 2 Poliovirus Vaccines on March 27, 1962. This was followed by the issuance of a license for type 3 Poliovirus Vaccine to Wyeth Laboratories on May 17, 1962. The pressures for vaccine to implement springtime immunization programs meant that the control facilities were strained to the limit. The need for serums with high antibody levels to permit the detection of SV-40 in preparations containing at least $10^{7.0}$ $TCID_{50}$ of poliovirus per milliliter was met by concerted efforts of the staff of this laboratory. Be early September when most of the demands had been met, analyses of the surveillance data showed that disease had occurred in some persons, mostly adults, who received the type 3 vaccine. This situation required action by the Surgeon General, who advised that the type 3 vaccine henceforth be given only to children. This action halted the release of all type 3 vaccines after September 6, 1962, and served to stimulate increased production of the Salk Vaccine by certain manufacturers.

The situation with respect to adenovirus vaccine remained quiescent during the period of this report. All of the manufacturers were attempting to prepare seed viruses free of extraneous viral agents. This work proceeded very slowly and only by the end of this period were reports received indicating that some success was being attained.

Methods for the standardization of immune serum globulin preparations were worked out and surveys of antibody content of a number of preparations permitted the draft of Regulations for their products. This draft is now under discussion by scientists of various interested laboratories.

The appearance of measles vaccine, both the living, attenuated and the killed virus preparations, on the horizon of licensed biological products, brought rearrangement in testing responsibilities. The killed virus vaccine

was added to the program of both the tissue culture section and the pathology section. The live, attenuated virus vaccine was made an additional responsibility of the pathology section. Increases in personnel in both these sections are now being implemented in order to meet these new duties.

The control program for poliomyelitis and adenovirus vaccine involved the following examination and release actions:

Poliomyelitis Vaccines		Adenovirus Vaccines
Samples Received	76	11
Vaccines Released	58	11
Combined with other Antigens	26	0
Vaccines Rejected	0	1
Vaccines Withdrawn by Mfr.	7	0

The control program for Poliovirus Vaccines, Live, Oral, involved the following examination and release actions:

	Type I	Type II	Type III
Samples Received	39	38	42
Vaccine Released	31	42	24
Vaccines Rejected	1	0	1
Vaccines Withdrawn by Mfr.	4	1	6
Vaccines submitted for consistency purposes	0	0	2

The research program of the laboratory has included work by Dr. Kirschstein and her collaborators who showed that ependymomas were produced in newborn hamsters after intracerebral inoculation of SV-40. In mastomys, however, it was found that ependymomas occurred following subcutaneous inoculation. Additional work with SV-40 revealed that some transformation of normal adult human thyroid cell cultures was produced by the virus. Carrier cultures resulted which had the capacity for limited growth when inoculated into the brains of monkeys. Virological studies by Dr. Gerber indicated that at least $10^{6.5}$ $TCID_{50}$ of SV-40 were needed to produce ependymomas in newborn hamsters. The virus could be recovered from intact tumor cells but not from extracts of the tumors.

In a study of samples of Salk poliomyelitis vaccine which had been stored at 4° C for 5 to 7 years, Dr. Gerber found that SV-40 was detected in tissue cultures which were inoculated with 16 of the 32 samples studied. Thus, another demonstration of the remarkable stability of this virus has been made.

Changes in personnel continue to play an important part in meeting our responsibilities. During the past year Dr. Gerald Van Hoosier and Dr. Gerald Borman resigned their positions in the Commissioned Corps in order to work in research at academic institutions, the former at Baylor University and the latter at Johns Hopkins University.

Again this year the Laboratory of Virology & Rickettsiology undertook a wide variety of studies ranging from field work centered around the first attempt to eradicate measles from a nation to exploratory studies on natural defense mechanisms which assist the infected cell in eliminating intracellular pathogens.

Measles: Although licensed live attenuated measles virus vaccine has not yet become available, extensive work has been done in the United States and elsewhere with experimental vaccines produced in commercial facilities. The experience in the field and in the research and biologics control laboratories has accumulated to the point where a licensed commercial product can be anticipated shortly.

The Section on General Virology has made substantial contributions to the development of reference standards and procedures applicable to the biologic control of both live attenuated measles virus vaccine and inactivated measles virus vaccine and of human gamma globulin which may be used along with the attenuated measles virus vaccine in the immunization of children.

The SGV has added materially to knowledge regarding the use of live attenuated measles virus vaccine through its studies in West Africa. These, undertaken as a collaborative venture by the DBS, the Ministry of Health in Upper Volta, and the AID have demonstrated that Voltan children respond in the same manner as American children to the live vaccine, whether given alone or in combination with gamma globulin. Because measles is one of the serious diseases of Upper Volta, with mortality rates running as high as 50% at times, and because the Volta health officers and the people do not object to the mild illness which is common when attenuated virus is given without gamma globulin, plans were made for a large-scale measles vaccination program in Upper Volta using attenuated virus alone in all children under the age of three years. This represents the first attempt to eradicate measles from a nation. The original plan called for the inoculation of 100,000 children. Before the plan became operative in early November 1962, this was raised to 300,000* on the basis of a new census of the population. At the moment it looks as if the actual number to be vaccinated will be appreciably more than a half million. Vaccine is being administered parenterally by jet injection by teams which comb the country, district by district. Each team consists of three indigenous Voltans employed by the Ministry of Health and is equipped with a jeep, two jet guns, an electric generator for operating the guns, and a portable refrigerator for transportation of the vaccine. Each of the eight teams, which cover a limited area before moving on, is visited every 2-3 days by the DBS investigators (Drs. Meyer and Hostetler and Mrs. Bernheim) who advise and assist in the work. During the first 3 weeks of the mass immunization program over 200,000 children were inoculated. The plan is to complete the work by the first of February 1963, which is the beginning of the annual severe measles epidemic in this region.

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*The number actually given measles vaccine by the time the program was completed in early 1963 was 730,000.

The effort to date has been most encouraging. The acceptance of the immunization procedure by the mothers is little short of amazing. When the word goes out that measles vaccination is to be done at a certain time and place, mothers walk in for miles, carrying their children. The populace does not view all immunizations with such enthusiasm. Indeed, sometimes the health officers who arrive for other purposes are chased out of the villages. In the first 200,000 Voltan children inoculated, serious complications have been recorded in only one instance; this was a spreading cellulitis which began at the site of jet injection and, in the absence of medical care, eventually resulted in death. While the ultimate success of the mass immunization program will be judged by the reduction in measles during the forthcoming annual epidemic, it is already apparent that the experience has provided worthwhile information on the means by which measles immunization can be accomplished in a developing nation when accompanied by the enthusiasm of the people and of the government of the country.

Before launching the mass-vaccination program mentioned above, the DBS team undertook a second series of pilot studies in which live attenuated measles virus vaccine was used in combination with smallpox vaccine and yellow fever vaccine administered by jet injection. Besides their scientific value, the pilot studies provided an opportunity for the Americans to train the Voltan teams who were to carry out the mass program. The studies indicated that a bivalent vaccine (dried measles and smallpox vaccines rehydrated separately and mixed just prior to connecting to the jet injection apparatus) and a trivalent vaccine (measles, smallpox and yellow fever mixed in the same manner) can be used without untoward effects in Voltan children. Serological tests to determine the response of the children to the mixtures of attenuated viruses remain to be completed. However, it is worth noting that previous experience had indicated that American children responded satisfactorily to a combination of measles and vaccinia viruses and American adults to a combination of vaccinia and yellow fever. If such polyvalent living vaccines prove to be immunogenic and safe, their use would be welcomed in developing countries.

Avian Leukosis Virus Complex and the RIF Test. Studies on the avian leukosis virus complex and Rubin's Rous interference factor (RIF) test were initiated early in the calendar year. In developing the regulations for live attenuated measles virus vaccine, which is prepared from virus grown in chick embryo tissue cultures, a safety test was included to ensure that viruses of the leukosis complex were not present in the vaccine. The only feasible control test for this purpose in the present state of knowledge is that described by Rubin -- the RIF test. In principle it is simple. Wild viruses of the complex, including wild strains of Rous sarcoma virus, grow in chick embryo tissue culture monolayers without producing obvious signs of their presence. However, when present and growing in the monolayer, they interfere with the production of proliferative and degenerative foci which are elicited by an appropriate laboratory strain of Rous virus.

The complexities of the test are multiple, but two are outstanding. Tissue cultures prepared from embryonated eggs from most chickens are contaminated with avian leukosis virus, hence are unsuitable for the RIF test. Another difficulty with the RIF test is that it must be carried through three serial passages beyond the primary chick culture which was inoculated with the unknown, and then challenged with Rous virus before results can be obtained

indicating that the test material is free of leukosis agents. The LVR was interested in the RIF test only as a control procedure in the safety testing of measles vaccine, nevertheless it was forced into investigative and developmental work on the RIF test because no other laboratory in the NIH had successfully employed the procedure.

During the year, a task force was drawn from various units in the LVR to establish Rubin's test on a working basis. After this was accomplished a permanent unit was established, under Mr. Jahnes, in a newly-converted laboratory in the Section on Basic Virology and Rickettsiology to do the necessary biologics control testing and to investigate the role of this group of viruses in vaccines.

Hepatitis. Dr. O'Malley continued studies on the properties of the A-1 virus, an agent presumed to be causally related to some cases of homologous serum jaundice. Work reported previously had shown that jaundiced volunteers developed A-1 antibodies. Serologic studies on volunteers who failed to develop jaundice after inoculation with proven icterogenic materials suggested that these persons had had previous experience with A-1 virus and that this might account for the failure of clinical disease to appear.

Paired serum specimens from 40 persons receiving multiple blood transfusions failed to show the development of A-1 virus antibody. Only one of these 40 patients developed jaundice within a 3-month post-operative period; serum specimens taken from this person up to 3 months after onset of jaundice did not contain A-1 virus antibody.

Tests on 400 convalescent serum specimens from patients in outbreaks of infectious hepatitis revealed that 18 or 4.5% contained A-1 virus antibody. This antibody was also found in 4 of 44 specimens from persons who were considered to have serum hepatitis. However, of the 40 specimens in the latter group which contained no A-1 virus antibody, 12 were taken at a time too early for antibody to have appeared and 26 were taken 9 or more months after jaundice. Previous findings had demonstrated that this antibody usually decreases to undetectable levels within nine months. Data were unavailable regarding the phase of the disease at which the remaining 2 specimens were drawn. Thus, A-1 virus antibody was found in 4 of 6 specimens in which it might have been expected to have occurred.

Continuous Cell Culture Lines. The BS-C-1 cell line, initiated in March, 1960, from kidney tissue of Cercopithecus aethiops by Mrs. Hopps of the Section on Basic Virology and Rickettsiology, is now in its 125th passage and is considered to be an established cell line. Cultures have been sent to the Cell Bank Committee (sponsored by NCI) for characterization and subsequent storage at the American Type Culture Collection. The BS-C-1 line is unique in that this is the only reported continuous culture whose chromosomal pattern and virus susceptibility have been studied in concert since early passage levels. Findings indicate that while the chromosomal pattern of the cells changed from diploid (30th passage) to subdiploid (at 41st passage) to heteroploid (111th passage), the cells have not changed their sensitivity to SV-40 virus. Moreover, at the 108th passage they were still sensitive to attenuated measles virus. Further evidence of their stability with regard to virus proliferation was noted in studies with influenza A and B and adenoviruses 3, 4 and 7. The BS-C-1

line was refractory to these agents at low passage and still failed to support their growth at the 95th passage level. In addition to those viruses already reported to multiply in BS-C-1 cells, i.e., SV-40, measles, and attenuated polioviruses 1, 2 and 3, it has been shown that this line will support growth of Rift Valley fever virus, RS virus, O'Malley's A-1 agent, Coxsackie A9, and simian viruses 1, 4 and 5 but not SV-2. Moreover, preliminary data suggest that the line may be useful in basic studies with epidemic typhus rickettsiae. The cell line has come into general use in the scientific world; 46 research and industrial laboratories in North America, Europe, Asia and Australia were supplied on request with seed cultures during the year.

Among the numerous technical difficulties inherent in the present RIF assay procedure is the necessity for a continuous supply of known RIF-free chick embryos. The establishment of a RIF-sensitive chick embryo tissue culture line would solve one of the major problems in measles vaccine testing. Selected chick embryos, presumed to be RIF-free, were employed in attempts to develop a useful cell line. In only one of 17 attempts has the cell culture survived beyond the 18th passage. This line, BS-CE-17, is now in its 31st passage but its growth rate has decreased and survival of the line is questionable.

Rickettsial Vaccines. Work on rickettsial vaccines continued in the SBVR-SRV during the year but at a slow pace because of diversion of efforts to problems connected with measles and respiratory vaccines.

As a result of the collaborative work undertaken in the military services last year in which groups of marines were inoculated with progressively diminishing doses of commercial vaccine, changes are being made in the primary course of immunization against typhus employed by the military services. Instead of two doses of 1 ml. each, the primary course will consist of a single dose of 0.5 ml. Additional studies using marine recruits are in progress to determine the minimal amount of typhus antigen which will induce a state of immunological preparedness in young adults so that they will subsequently respond in a booster fashion when given typhus vaccine prior to exposure in epidemic areas.

A collaborative field study using a pilot lot of formalin-inactivated Q fever vaccine prepared at the Walter Reed Army Institute of Research is in progress in several areas of the USA. This is designed to determine the value of a course of immunization which hopefully will prevent previously sensitized persons from developing untoward reactions. Draft regulations for the manufacture of Q fever vaccine have been developed in the LVR, circulated to manufacturers and investigators, and are now being prepared in final form for publication. Reference vaccine and antisera for use in assaying the potency of Q fever vaccine are on hand.

Influenza. In the winter of 1961-62, sporadic outbreaks of influenza occurred in Japan, Taiwan and New Zealand, during which a number of Asian strains were isolated by workers in several monitoring laboratories located in these areas. Some of the strains were sent to the Division for antigenic analysis. The results obtained by Dr. J. A. Morris and his associates in the Section on Respiratory Viruses in hemadsorption-inhibition tests performed in cell cultures and in neutralization tests performed in mice, indicated an extensive shift in

antigenic composition in some of the 1961-62 Asian strains away from the prototype A2/Japan/305/57 contained in the present vaccine.

Antigenic analysis of influenza B strains recovered in the winter of 1961-62 in outbreaks of influenza in the United States and Canada indicated a clear, but relatively small, antigenic difference between the recent strains and the older strains contained in the current vaccine.

Thus it appears that a major antigenic change has occurred in recent isolates of A2 viruses and a minor shift in B viruses as compared with strains of previous years. These findings were presented to an ad hoc group assembled at the DBS on December 2 to advise on strain composition of influenza vaccine. Following analysis of the data just mentioned and other information provided by those in attendance, it was recommended that one of the new A2 strains and one of the recent B strains be incorporated into the vaccine which will be manufactured for the 1963-64 season. Steps are being taken to determine whether the two strains tentatively selected for inclusion are suitable for production and are antigenic in man.

Arboviruses. A member of the LVR organized and chaired a symposium on "Immunization Against Arbor Virus Infections" held at the annual meeting of the American Society of Tropical Medicine and Hygiene. Progress in this field has been reasonably rapid, but except for an inactivated Rift Valley vaccine, prepared from monkey kidney tissue cultures by techniques analogous to those used in manufacturing Salk vaccine, none of the new vaccines or procedures is apt to require serious consideration by DBS as regards the development of regulations and control procedures for license within the next year or so.

Antimicrobial Substances. Dr. C. P. Li and his group in the Section on Virus Biology continue to devote most of their efforts to the study of the antibacterial and antiviral substances obtained from oysters and other mollusks and have extended their survey of antimicrobial substances of plants and animals. Several psoralen compounds which were identified years ago in fruits and subsequently used in man to accelerate suntanning have some activity against several viruses in tissue cultures and in mice.

Administrative Changes. Dr. Motoichi Hatano, of the Kanazawa University, Kanazawa, Japan, joined the Section on Respiratory Viruses in January of 1962 as a Visiting Scientist. Dr. Seiya Kohno of the National Institute of Health, Japan, who has a Rockefeller Fellowship, was a Guest Worker during the year in the Section on Basic Virology and Rickettsiology. Dr. Anan Nisalak continued as a guest worker in the Section on Basic Virology and Rickettsiology for the first 6 months of 1962.

On July 1, Dr. Eddy and her Section on Experimental Virology, with its personnel, equipment and space, were transferred from the Laboratory of Virology and Rickettsiology to the Office of the Director, DBS.

Dr. Lewellys F. Barker joined the Section on Basic Virology and Rickettsiology on July 1, 1962.

LABORATORY OF BIOPHYSICS AND BIOCHEMISTRY

Research activities of the laboratory continue to be identified primarily with the application of physical principles to microbiological systems. An extension of an earlier study of photochemical processes affecting survival of viruses has led to the development of a photosensitization technique for differentiating between parent and progeny virus in cell cultures. This technique has made it possible to detect multiplication of poliovirus in non-primate cells that were previously thought to be refractory to infection. This finding has some bearing upon the developing concepts of the relationship between viruses and their animal hosts. Other aspects of the subject are pertinent to the development and control of viral vaccines, since the opportunity of cultivating poliovirus serially in novel media will add to our information about properties of various strains.

The staff of the Laboratory of Biophysics and Biochemistry has been supplemented by the addition of two scientists during 1962. Dr. Nobuto Yamamoto, a Japanese biophysicist, appointed as Visiting Scientist, is investigating the mechanism of photodynamic inactivation of bacteriophages with the expectation that this information will eventually contribute to our understanding of viral genetics. Dr. John M. Easton, a medical officer with special training in micropathology, has undertaken an electron-microscopic study of the cytopathic effects of simian viruses on monkey kidney tissue culture cells. Dr. Easton's prior experience with the ferritin-tagging technique for visualizing antigen-antibody complexes in the electron microscope will be an asset in this investigation.

Mr. Andrew M. Young, who recently obtained the M. S. degree in chemistry at Temple University, has replaced Mr. Raoul Benoit in the physical instrumentation unit of this laboratory. Mr. Young will be in charge of the analytical ultracentrifuge and associated equipment.

LABORATORY OF BLOOD AND BLOOD PRODUCTS

Research Activities. The research program of the Laboratory of Blood and Blood Products during 1962, with the exception of work on coagulation components, has been at a virtual standstill as a result of the forced diversion of professional staff time to a major investigation of possible violations of the Public Health Service Act. This also caused considerable disruption of routine duties because of the top priority necessarily assigned to the investigation. The objectives of the research program of the Laboratory remain unchanged, though more than a year's effort toward attaining these objectives has been lost. Hopefully the requirements for staff time to assist the U. S. Attorney in the prosecution of these cases will soon be much less and the research program can be pursued.

The various fields of interest have as their goal the improvement of testing procedures used for the control of biological products derived from blood; these procedures being designed in so far as possible to insure the safety, purity and potency of the products. The projects cover all phases of blood collection, processing, shipment and storage. Investigations encompass not only improvements for existing control procedures but also are directed toward the perfection of new tests for existing products as well as for new products.

There is at present much interest in the components of the coagulation system. Some of the new products under development have immunological or biological activities for which there are no established test criteria. The urgency imposed by this interest and the lack of testing methods demanded that work continue on coagulation components. This was the only project that received significant attention during 1962 and research on some of the fundamental characteristics of these proteins was continued to gain information on which useful control tests might be based. Further improvements have been made in the method of preparation of a plasminogen free fibrinogen; an important accomplishment since it brings us one step closer to the goal of control tests for the complex coagulation system that are independent of the reagents used.

Other research interests of this Laboratory include:

Studies of freezing, storage at various low temperatures, thawing and/or drying of the many elements of whole blood and protein fractions of plasma. Specific investigations within this broad field are undertaken to obtain data on which to base dating periods and stability of products.

For many years, the Laboratory has maintained an active research interest in the effect on the properties of whole plasma and the individual plasma proteins of time, light, container material, temperature fluctuations and other factors. Normal Serum Albumin was placed on such a long term study eight years ago. Subtle changes occur which have been taken into account in establishing a dating period schedule for this product.

Immunological studies related to the identification and quantitation of antigens on red blood cells and other formed elements and of the antibodies which occur in blood continue to intrigue the professional staff of the Laboratory. Many control tests still have an empirical basis. An ultimate goal of these immunological investigations in control tests which result is realistic quantitative expressions of identified antibodies or antigens.

"Extramural" Research and Other Activities. The "extramural" program of this Laboratory is not formally organized in the sense of extramural programs of other Institutes but nevertheless contributes to the research aims of the Laboratory. Because of the nature of the control functions of the Laboratory, many contacts are made with scientific staffs of outside organizations for various reasons.

It is the duty of the staff of the Laboratory to be aware of advancements in all areas of blood technology. To this end, staff members regularly visit and consult with other laboratories, attend meetings in fields of their specialties and present the results of their own research.

Somewhat related to this is the participation by members of the Laboratory staff in blood bank workshops and training programs. This activity, while performed on an informal basis, nevertheless allows more efficient dissemination and illustration of blood banking techniques. Techniques are being explored that will allow greater participation by the Laboratory's trained staff in these training programs as a contribution to the raising of the standards of achievement of blood banks.

The Laboratory will continue its cooperation with American Standards Association and the International Standards Organization in studies of the interchangeability of disposable blood equipment.

As one means of speeding the flow of specific research information and material, the Laboratory is planning to make use of research contracts. Under active negotiation at the present time are contracts designed to yield needed information or reagents on the following subjects:

1. Evaluation of the anti-human complement component of an anti-human globulin serum for the Coombs test.

2. Establish more realistic standards for ABO grouping serum.

3. Prepare anti sera to specific proteins for use as reagents in immunological control procedures and as standards.

4. Design and build a variable rate feed pump for special applications in chromatography.

5. Establish the quantitative significance of A and B antibodies in pooled plasma.

6. Prepare additional blood antigen antiserums for use as reference preparations.

7. Prepare fibrinogen and thrombin by a specified method for use as reference preparations.

8. Prepare anti-hemophilic factor for use as a reference preparation.

Budget in Support of DBS
1962 Annual Reports

	Amount
Program Direction (Office of Director, Technical Services, Administration, Research Contracts)	$389,000
Auxiliary	133,000
Experimental Virology	33,000
Lab. of Control Activities	380,000
Lab. of Bacterial Products	180,000
Lab. of Blood & Blood Products	290,000
Lab. of Virology & Rickettsiology	492,000
Lab. of Viral Immunology	626,000
Lab. of Biophysics & Biochemistry	108,000
Total DBS direct operations calendar year 1962.....	$2,631,000

PHS-NIH
Individual Project Report
Calendar Year 1962

Program direction and administration for the Division of Biologics Standards is centered in the Office of the Director, with centralization of administrative procedures relating to personnel, travel, supply and accounting. Major objectives are determined and program responsibilities are assigned to the operating units within the Division. For each major area, staffing patterns are developed and are continually reevaluated in relation to program changes. The required financial support is determined for each area in relation to the Division's total budget. A major activity of the Office of the Director is the maintenance of the proper balance between the control activities and the research programs, the latter being supported to the degree that such investigations are required in order to meet the control responsibilities of the Division.

The Director working with members of his immediate staff, including a legal assistant, conducts a continuing review of existing regulations for the control of biological products, making revisions as necessary and also develops additional regulations as required for new products.

During 1962, the Office of the Director expanded its technical function in the field of statistics when Dr. C. J. Maloney joined the staff. This nucleus will be enlarged to include approximately six persons and will operate as a Section on Statistics within the Office of the Director.

Another technical change was the transfer of the Section on Experimental Virology from the Laboratory of Virology and Rickettsiology to the Office of the Director.

Close and continuous liaison is maintained with technical representatives of industry. Frequent meetings are held between members of the Division's professional and administrative staff and individual manufacturers and groups of manufacturers who are concerned with common problems (these occasionally take the form of conferences which also involve outside consultants to the Division). In addition, approximately 200 conferences are held each year with technical representatives of manufacturers who desire to discuss production and testing programs peculiar to their own organization.

The Office of the Director services the Board of Scientific Counselors, the Technical Committee on Poliomyelitis Vaccine, the Public Health Service Committee on Live Attenuated Poliomyelitis Vaccine, as well as numerous Ad Hoc Committees which are appointed from time to time to consider matters relating to the control of biological products.

Within the Office of the Director, the Information Office continues to be concerned with, (1) communications through such media as press, radio, television, publications and exhibits of information to the public on the Division's control and research activities, and (2) internal communication of such information through reports to the Director, NIH, and to the Surgeon General as well as to the Department and to the Congress.

During 1962 considerable effort continued to be devoted to: 1) enforcement activities in the blood and blood products field; 2) problems relating to measles vaccines; and 3) the licensing of live poliovirus vaccine, type 3.

The resources of the Division continue to be heavily taxed by the growing workload. It has been possible to meet these increased demands by diverting personnel and resources from projects of lower priority and by postponing investigations in other areas. Increased support has been requested, but full and efficient implementation of the support will only be possible when the planned additional facilities become available to the Division with the completion of the new building estimated to be in June 1965. Funds for the planning of the building became available in 1962 and with the conclusion of a contract with an architectural and engineering firm for designs and plans, the Office of the Director became heavily involved in work related to the new structure.

Serial No. DBS 2
1. Experimental Virology
2. Office of the Director
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A.

Project Title: Experimental Virology

Principal Investigator: *Dr. Bernice E. Eddy

Other Investigators: None

Cooperating Units: None

Man Years:
Total: 2 3/4
Professional: 1
Other: 1 3/4

Patient Days: None

Project Description:

The over all aim of this project is to investigate the safety of biological products, to study viruses that may serve as models for improving existing vaccines, to investigate new viruses for the purpose of exploring the possibility of preventing diseases that at present are uncontrolled and to fulfill the obligation of controlling anti-pneumococcus sera. Due to space and personnel limitations, of necessity only a limited number of viruses could be used. The viruses used were: the papova viruses, adenoviruses and miscellaneous or unclassified viruses.

Serial No. DBS 3
1. Experimental Virology
2. Office of the Director
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A.

Project Title: Experimental Virology (papova viruses)

Principal Investigator: Dr. Bernice E. Eddy

Other Investigators: None

Cooperating Units: None

Man Years:
Total: 1 5/12
Professional: 2/3
Other: 3/4

Patient Days: None

Project Description:

Work on one member of this group of viruses was started several years ago in an effort to gain information on the etiology of lung cancer and as a sideline in investigations of the known respiratory viruses. The original objective was to find a way to isolate a virus or viruses from human neoplasms and to find a way to prevent neoplasms in man. This is still an objective but it has been shelved for the present because of the importance of one of the papova viruses, simian virus 40 which is a contaminent of rhesus monkey kidney cell cultures used in production of certain virus vaccines. An understanding of the properties of the papova viruses may aid in investigations of other oncogenic or latent viruses. The immediate aim of the project will be to continue to study the properties of this group of viruses for the purpose of 1) determining the most effective way to detect and eliminate simian virus 40 and 2) to gain information that might be useful in investigations of human cancer viruses.

The activities include:

(a) Determined the effect of certain physical and chemical agents, route of injection, age and animal passage on induction of neoplasms in hamsters by simian virus 40.

(b) In collaboration with Dr. Roger Weil at the California Institute of Technology extracted nucleic acid from purified simian virus

40 and studied its chemical and biological properties. These studies are not complete.

(c) In collaboration with Dr. Klaus Bayunther at the California Institute of Technology began an investigation of the transforming capacity of simian virus 40.

(d) With Dr. Karl Habel in the National Institute of Allergy and Infectious Diseases. started a study on an immunological comparison of simian virus 40 and polyoma virus induced neoplasms.

(e) Cell cultures from animals other than monkeys were infected with simian virus 40 and the cultures are being observed for morphological changes and for oncogenic activity in hamsters.

Work with these viruses is being continued in an effort to obtain information that may be useful for the over all project.

Serial No. DBS 4
1. Experimental Virology
2. Office of the Director
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A.

Project Title: Experimental Virology (Adenovirus)

Principal Investigator: Dr. Bernice E. Eddy

Other Investigators: None

Cooperating Units: None

Man Years:
Total: 2/3
Professional: 1/6
Other: 1/2

Patient Days: None

Project Description:

The objective of work with this group of viruses is to imporve methods for evaluating the purity and safety of adenovirus vaccines and of assessing the oncogenic capacities of some of the types of adenoviruses.

The activities include:

(a) On purity of adenovirus vaccines. Adenovirus vaccines, some known to contain SV 40, others in which no SV 40 had been detected were injected into newborn hamsters. A subcutaneous neoplasm developed in a hamster that had been injected with one lot of vaccine. The remaining animals are under observation.

(b) Oncogenic capacity of adenovirus, Type 12. The oncogenetic activity of adenovirus Type 12 reported by scientists at Baylor University was confirmed and the properties of this virus are being compared to the properties of some of the papova viruses.

Work with the adenoviruses is being continued to learn more about purification of these viruses and to obtain more information on their relationship to neoplasms.

Serial No. DBS 5
1. Experimental Virology
2. Office of the Director
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A.

Project Title: Experimental Virology (Miscellaneous viruses)

Principal Investigator: Dr. Bernice E. Eddy

Other Investigators: None

Cooperating Units: One phase--Laboratory of Physical Biology, DBS

Man Years:
Total: 2/3
Professional: 1/6
Other: 1/2

Project Description:

The aim of this part of the project is to study new or little understood viruses, their hosts and pathogenic potentialities in order to obtain information necessary for investigating diseases of unknown etiology.

The activities include:

Different viruses have been studied from time to time but the so-called "foamy viruses" have received most attention. This group of viruses infect different primates. They are difficult to propagate and progress has been slow. Dr. C. W. Hiatt and Mr. John Thiel are cooperating in a study of the morphological characteristics of these viruses.

Work on these viruses is being continued in order to obtain information that will be useful in investigations of diseases of unknown causes.

Serial No. DBS 6
1. Experimental Virology
2. Office of the Director
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A.

Project Title: Pneumococci

Principal Investigator: Dr. Bernice E. Eddy

Other Investigators: None

Cooperating Units: None

Man Years:
Total:
Professional: Insignificant

Project Description:

The objective of the project is to control pneumococcus typing sera. This is a minor project; only two lots of pneumococcus typing serum mixtures were released in 1962.

The activities include:

Each lot was tested for potency for one or more of the component homologous types.

The major aim of the project is to fulfill the obligation of controlling pneumococcus typing sera.

Serial No. DBS 6

1. Experimental Virology
2. Office of the Director
3. Bethesda, Maryland

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Part B. Honors, Awards, and Publications

Publications other than abstracts from this project:

(1) Eddy, B. E., Borman, G. S., Grubbs, G. E. and Young, R. D. Identification of the oncogenic substance in rhesus monkey kidney cell cultures as simian virus 40. Virology 17:65-75, 1962.

(2) Eddy, B. E. Comparison of the properties of two viruses oncogenic for hamsters, simian virus 40 and the polyoma virus. Perspectives in Virology 3: In press.

(3) Eddy, B. E. Tumors produced in hamsters by simian virus 40. Fed. Proc. In press.

(4) Eddy, B. E., Grubbs, G. E. and Young, R. D. Persistent infection of human carcinoma and primary chick embryo cell cultures with simian virus 40. Proc. Soc. Exp. Biol. & Med. In press.

Honors and Awards relating to this project:

At least seven invitations to participate in or to present papers at meetings and conferences of national and international significance.

Serial No. DBS 7
1. Control Activities
2. Office of the Chief
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A.

Project Title: Office of Chief, Laboratory of Control Activities

Principal Investigator: Dr. W. G. Workman

Other Investigators: None

Cooperating Units: Three

Man Years:
Total: 5½
Professional: 1
Other: 4½

Patient Days: None

Project Description:

Under the direct supervision of the Director, Division of Biologics Standards, this Laboratory carries out activities directly with licensed manufacturers of biological products relating to their establishment and product licenses and to the control of biological products manufactured and distributed by them. These activities are supported by sections on reference standards, on control tests, and on pyrogens.

The activities include:

(a) Determination of eligibility of establishments and of individual biological products for license. This determination is made on the basis of a review of the integrity of management, of the physical facilities for manufacture and testing of products, of the scientific and professional qualifications of personnel, and of the evidence of continued safety, purity, and potency of products for which an application for license is being evaluated. Recommendations for establishment and product licenses are usually made by an ad hoc committee consisting of appropriate members of the staff of the Division, but the Chief of the Laboratory reviewsall such recommendations and accepts full responsibility for them.

(b) Supervision of annual and special inspections of licensed manufacturers and of establishments for which an application for license has been made.

(c) Releasing of individual lots of biological products for distribution by manufacturers on the basis of review of manufacturer's tests, of tests made in the Division, and of other data relating to the safety, purity or potency of the individual lot of the product.

(d) The establishment and distribution of physical biological standards, reference preparations and control materials. A small culture collection is also maintained mainly for the Division and licensed manufacturers.

(e) Review of requirements and Regulations now in effect for such constructive revision as is needed and development of requirements and Regulations needed for new products.

(f) Maintenance of close working relations between this Laboratory and the other Laboratories of the Division in order to insure continous knowledge of all activities and information needed for licensing of establishments and of new products and for the testing, release and control of individual lots of products currently licensed.

(g) Serving on various committees and collaborating with other official or non-official agencies concerned with the manufacture, testing, control or use of biological products.

(h) Cooperation with other government agencies particularly the Department of Defense for interchange of information relating to the control of biological products and their use in preventive medicine.

(i) Maintains contacts with other workers in preventive medicine in this country and abroad.

Significance to Division of Biologics Standards: This project is directly related to the legal responsibilities and administrative functions of the Division, and requires close liaison with the research activities of the Division in order to put new knowledge to practical use.

Proposed Course of Project: It is proposed to continue the activities of this Laboratory as at present with due emphasis on improvements in control testing procedures, on the development and use of reference standards and on more useful requirements for products.

Serial No. DBS 8
1. Control Activities
2. Control Tests
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A.

Project Title: Control Testing and Investigations Related to Control of Biological Products.

Principal Investigator: Mr. Robert W. Kolb

Other Investigators: Mr. Otis L. Green
Mr. Harry T. Aylor

Cooperating Units: None

Man Years:
Total: 10
Professional: 2
Other: 8

Project Description:

The principal objective of this project is to assure the compliance of licensed biological products with standards established under the biologics control provisions of the Public Health Service Act. Individual lots of biological products are recommended for release on the basis of evaluation of the manufacturer's and Division of Biologics Standards tests. The evaluation includes control testing for sterility, safety, potency and purity as required for licensed biological products including antitoxins, therapeutic immune serums, blood and blood derivatives, bacterial vaccines, toxins and toxoids, multiple antigens, viral and rickettsial vaccines, diagnostic substances for dermal tests, antivenins, venoms and allergenic extracts. Supplemental to control testing are the following activities: (a) Evaluation of manufacturers' protocols of tests on lots of biological products for compliance with minimum standards; (b) preparation of releases; (c) maintenance of a permanent record and filing system for releases, protocols of manufacturers' tests, and samples of all biological products submitted to the Division and (d) a continuing reevaluation of methods and operations relative to the establishment of efficient control measures.

In addition to the above activities are a number of research and other functions which have been related to this program as follows: (a) Research dealing with the development of new methods for the

control of biological products and designed to improve existing in vivo and in vitro methods of testing; (b) research concerned with the study of stability of biological products and with the development and standardization of new biological preparations; (c) participation in the establishment and product licensing program, which involves the review and screening of new license applications, testing of products submitted in support of such applications, prelicensing inspections and preparation of official reports; (d) participation in the annual inspection program of licensed biological establishments and the control testing of inspection samples collected; (e) participation in the revision and formulation of regulations and additional standards for biological products; (f) cooperative investigations with intraagency laboratories, commercial establishments, domestic and foreign governmental agencies in which studies and assays are carried out on numerous biological and pharmaceutical preparations; and (g) the orientation and training of new government personnel and visitors from other domestic and foreign health laboratories and institutions in biological control testing methods and related operations as conducted within the Division.

Major Findings and Accomplishments:

I. Control Testing Activities

(a) During the past 12 months (i.e., December 1, 1961 through November 30, 1962) biological products have been tested for conformance to Public Health Service standards and regulations. A total of 7,007 control tests were carried out in the laboratory of Control Activities to insure the sterility, safety, potency and purity of licensed biological products. These are summarized as follows:

Products for Release.....	6,103	Tests
Inspection Samples.....	886	"
Complaint Investigations.....	18	"
Total	7,007	"

The data obtained served as the bases of recommendations for acceptance or rejection of the individual lots examined.

In addition, 1,193 cooperative service tests were done on biological products not licensed.

(b) Permanent record and filing systems for releases, protocols of manufacturers' tests and samples of all biological products submitted to the Division of Biologics Standards were maintained. During the same period indicated above 5,041 lots of biological products were submitted for release by licensed manu-

facturers. Of these 4,915 lots were released, 56 lots were rejected and 70 lots were withdrawn from consideration for release by the manufacturers.

In addition, new record, filing, and sample distribution systems were setup to include the handling of various types of Measles Vaccines being considered for license. A modus operandi for the efficient handling of Measles Vaccine protocols and a reporting system on the status of lots pending official action have been developed and put in effect. It is expected that these measures will help to simplify the release and control of the product.

(c) Conducted 5 complaint and 38 special investigations of biological products and matters related to control activities during the year. Written reports and recommendations for action were made to the Chief, Laboratory of Control Activities.

(d) Quality control evaluations were made during the year of data collected in official potency tests run on rabies vaccines, smallpox vaccines, typhoid vaccines, and poliomyelitis immune globulins. Statistical evaluations, tables and charts were made plotting the respective end-point reactions obtained with the NIH reference materials in the various tests. Results showed that most of the potency assays conducted fell within 2 standard deviation limits.

This information has been helpful in studying variable factors in the test systems, in considering possible modifications or improvements in the laboratory control methods, and in keeping check on the continued stability and effectiveness of official reference standards.

II. Research

In addition to the above control testing, 125 research experiments were carried out in connection with the various projects under way. Brief summaries of these studies are given as follows:

(a) The cooperative project with Dr. M. Barile, Laboratory of Bacterial Products, DBS, on the development and standardization of a reference diphtheria toxin for the Schick Test and the development of an accurate potency test procedure for this product was continued during the year.

In standardizing the toxin, potency was determined by guinea pig skin reactions (MRD) and guinea pig lethal

responses (MLD). Avidity of the toxin was determined by information obtained on antitoxin combining reactions (Lr and L+ assays) carried out at different concentrations and periods of reaction. Physical and chemical properties of the proposed standard were determined and compared with values for the International Standard Diphtheria Toxin.

The proposed potency test is currently being run with the official potency test to study its merits in the evaluation of commercial lots of Schick toxin submitted for routine release.

Reports on the above as well as a draft of additional Standards for Diphtheria Toxin for the Schick Test have been prepared and submitted to DBS for consideration and official adoption. These studies provide the necessary background information for the reevaluation and revision of present standards. It is anticipated that the proposed potency test involving the use of the Standard Diphtheria Toxin will be submitted to the manufacturers for trial and comment and that a report of the studies will be prepared for publication.

(b) The study on the standardization of an official U. S. Reference Smallpox Vaccine was continued during the year in cooperation with Dr. E. B. Seligmann, LCA. Additional experiments have been carried out comparing the potency of the proposed standard to that of a current NIH control vaccine, Lot 1b, as measured by the modified rabbit scarification and chick embryo techniques reported last year.

From the results of these studies and an evaluation of manufacturer's data on the use of the proposed reference, a revision of Minimum Requirements for Smallpox Vaccine was prepared. These requirements are to be sent to the manufacturers for comment.

(c) Studies were continued on methods of potency assay for the fluid diphtheria component of Tetanus and Diphtheria Toxoids Combined (For Adult Use) in order to extend standards to cover the product. Experiments to standardize a reference toxoid preparation for use in guinea pig antigenicity assays were continued. A suitable method for evaluating potency has been developed but further trials and evaluations of commercial preparations are necessary before written standards for the product can be drawn up.

(d) A study was initiated to compare the effectiveness of various laboratory methods for determining potency of BCG Vaccine. The problem is one of particular interest

because there has been an increase in requests for the licensing of BCG Vaccine and there is a need for revision of standards for the product. Vaccine viability counts by various microbiological cultural methods and animal sensitization experiments have been carried out. As more experience is gained with the testing and control of this product, it will be possible to advance recommendations.

(e) Participated in a collaborative study with Dr. Mealey, LBBP in the development of potency standards for human gamma globulin. A series of experiments were completed in the determination and comparison of the diphtheria and tetanus antibody titers of 23 experimental lots of globulin. Summary reports of the results were prepared and submitted for consideration.

(f) A field investigation was initiated during the past year to determine the efficacy of various tetanus toxoid preparations for use as single dose immunizing antigens in human subjects. This project further involves studies in which comparisons and correlations will be made of clinical and laboratory methods used in the potency evaluation of the various toxoids.

This laboratory in collaboration with Dr. Margaret Pittman, Laboratory of Bacterial Products has contributed to these studies. Experiments comparing the potency of the various toxoids tested by the official test methods have been carried out and the results and data from these have been submitted to Dr. Pittman for correlation with other data in the studies.

(g) Based on recent clinical reports concerning the stability and false positive reactions with diluted tuberculin preparations containing gum acacia, question arose as to whether skin sensitivity reactions also occurred in guinea pigs used in the official laboratory potency test for tuberculin. A brief study was carried out to confirm the validity of the official test method under these conditions. Results domonstrated that gum acacia in concentrations normally found in commercial tuberculin preparations did not produce skin sensitivity in guinea pigs or show false positive skin reactions in the official potency test.

III. Supportive Control Activities

(a) Numerous establishment and product applications were submitted for review and consideration for license during the year. Usually these are referred to ad hoc committees

for review. Personnel of this section participated in the review and processing 13 establishments and 61 product license applications. Also, involved was the control testing of the products submitted in support of these license applications. Complete reports and recommendations were submitted on each application.

(b) Participated in the annual inspection program of biological establishments by carrying out 3 special and 33 regular inspections. Official reports and recommendations were made on all establishments visited.

(c) Participated in the preliminary drafting of 1) standards and requirements for Diphtheria Toxin for the Schick Test and Smallpox Vaccine; and 2) dating periods for biological products.

(d) Ten visitors representing 8 foreign countries were given orientation and/or training in control testing and related activities during 1962. The length of the visitations ranged from several hours to 2 weeks.

IV. Proposed Course of Project

The proposed course is to continue the control testing, research and related programs with increasing efficiency and attempt to reach conclusions on research projects in as satisfactory and expeditious manner as possible.

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A.

Project Title: Investigations Related to the Establishment and Maintenance of Reference Standards for Biological Products.

Principal Investigator: E. B. Seligmann, Ph.D.

Other Investigators: Miss Jane Farber
E. C. Russell
W. H. Berkeley

Cooperating Units: None

Man Years
Total: 6
Professional: 2
Other: 4

Patient Days: None

I. Project Description:

Objectives: Since biological products cannot be standardized, with few exceptions, by chemical or physical means, recourse must be had to testing their effects in relation to physical reference preparations. It is the function of this project to provide these standard preparations for the use of manufacturers and others engaged in standardization in order to establish uniformity of potency throughout the country. It is largely by the use of these standards that those portions of the biologics law relating to potency can be enforced. A great deal of painstaking and responsible work is necessary to insure that standards issued are satisfactory as official standards for this country and bear a known relation to International Standards.

Methods Employed: Fluid preparations must be made and standardized from dried primary standards prior to the expiration date of the current lot. Old standards must be replaced as they become exhausted. Standards must be developed for new products and for certain of the older ones for which it has not been possible to prepare standards heretofore. This is dependent upon advanced knowledge in a number of fields, such as immunology, biology, biochemistry, and medicine and involves bacterial and viral biological products, allergenic extracts and blood products. Important features

of this work are the improvement of methods of preserving and storing standards, such as by freezing and drying, so that their potency may be maintained, selection or development of standard preparations which will yield clear-cut end points in control testing performed by all manufacturers, and correlation of these standards where possible with those established in other countries or with International Standards.

Major Findings and Accomplishments:

(a) In order to maintain an adequate supply of physical reference standards for use by the licensed manufacturers in their official control testing it is necessary to prepare and standardize new liquid lots from the primary dried stocks. The number of lots prepared and standardized during the year were antitoxins - 19, serums - 5, vaccines - 5, viruses - 1, toxoids - 3 and toxins - 3. A total of 701 tests were required to complete a satisfactory standardization of these lots. These tests include flocculation reactions, animal protection tests, animal potency tests, neutralization tests, and a number of specialized tests for specific products.

(b) Standard and Reference preparations and cultures are freeze-dried for greater stability during storage. This Section dried the following between November 15, 1961 and November 15, 1962:

Cultures	1340 ampules
Serums	1407 ampules
Vaccines	1837 ampules
Viruses	2630 ampules
Toxins	2146 ampules
Total	9960 ampules

(c) This Section distributed to commercial houses, health departments, universities, and foreign countries the following Standard and Reference preparations:

Antitoxins	500
Serums	1861
Vaccines	883
Toxins	356
Bacterial & Viral Cultures	2271

(d) A culture collection of organisms used in the production and testing of biological products is maintained by this Section. Official Standard,

Reference and Control preparations currently maintained are:

1. Standard Preparations

Bacterial Products

Botulinus Antitoxin, Type A
Botulinus Antitoxin, Type B
Diphtheria Antitoxin
Dysentery Antitoxin (Shiga)
Histolyticus Antitoxin
Oedematiens Antitoxin
Perfringens Antitoxin (Welchii)
Pertussis Vaccine
Opacity Standard for Pertussis Vaccine
Opacity Standard for Typhoid Vaccine
Scarlet Fever Streptococcus Antitoxin
Sordelli Antitoxin
Staphylococcus Antitoxin
Tetanus Antitoxin
Old Tuberculin
PPD of Tuberculin
Vibrion Septique Antitoxin

Viral Products

Antirabies Serum

Blood Products

Thrombin

2. Reference Preparations

Bacterial Products

Botulinus Antitoxin, Type C
Cholera Opacity Reference
Diphtheria Toxoid (AP)
Diphtheria Toxoid (Fluid)
Diphtheria Flocculating Serum
Haemophilus influenzae Typing Sera,
Types a,b,c,d,e,f
Histoplasmin
Nitrogen Reference
Plague Vaccine
Tetanus Toxoid (AP)
Tetanus Toxoid (Fluid)
Tetanus Flocculating Serum
Typhoid Vaccine
Typhoid Turbidity Reference

Viral Products

Adenovirus Vaccine Types 3,4,7
Adenovirus Crude Fluid, Type 3, Strain JF
Influenza Virus Vaccine, Civilian Formula
Influenza Virus Vaccine, Military Formula
Influenza Virus Vaccine for CCA Determinations
Measles Serum
Mumps Serum
Measles Virus
Poliomyelitis Immune Globulin
Poliomyelitis Serum
Poliomyelitis Vaccine, Type 1,2,3
Poliomyelitis Virus, Type 1
Poliovirus, Live, Attenuated
Rabies Vaccine
Rabies Challenge Virus
Rabies Production Virus
Smallpox Vaccine
Typhus Serum

Blood Products

Anti-A Blood Grouping Serum
Anti-B Blood Grouping Serum
Anti-Rh_o (Anti-D) Typing Serum
Blood Group Substances A & B
Coomb's Anti-Human Serum
Fibrinogen

3. Control Preparations

Bacterial Products

Antimeningococcic Serum
Hemophilus Influenzae Antiserum, Type b
Botulinus Toxin, Type A
Botulinus Toxin, Type B
Histolyticus Toxin
Oedematiens Toxin
Perfringens Toxin
Scarlet Fever Streptococcus Toxin
Sordelli Toxin
Staphylococcus Toxin
Tetanus Toxin
Vibrion Septique Toxin

(3) Yellow Fever Vaccine manufactured under U. S. Government license has been tested for conformance to the official regulations governing its production. A total of 202 lots were tested

for potency, 101 of which were tested for safety, during the year.

II. Proposed Course of Project:

An active research program has been initiated to provide basic data on the properties of existing and new standard preparations. A program designed to maintain a continuing, evaluation of the stability of each physical standard preparation is in effect. The improvement of existing preparations is a subject of continual investigation. Research directed toward the establishment of physical standards for products not now provided with an official standard for the potency test is being pursued.

III. Proposed Projects:

Continuation of projects already in progress.

IV. Projects in Progress:

(a) Basic research on the cultivation and assay of various strains of vaccinia virus in chick embryo.

(b) Improvement of the stability of dried rabies vaccine.

(c) Development of an improved reference tetanus flocculating serum and toxoid.

(d) Development of an improved reference diphtheria flocculating serum and toxin.

(e) Development of a satisfactory dried diphtheria toxin for all laboratory assay purposes.

(f) Development of an improved opacity standard.

(g) Correlation of opacity standard with various types of bacterial suspensions used in production and challenge.

Part B included Yes / / No /X/

Serial No. DBS 10
1. Control Activities
2. Pyrogens
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A.

Project Title: Section on Pyrogens

Principal Investigator: Harry W. Burruss

Other Investigators: None

Cooperating Units: None

Man Years
Total: 3
Professional: 1
Other: 2

Patient Days: None

Project Description:

The primary responsibility of this section is the testing of certain licensed biological products to determine their safety, purity, and stability as defined in the control regulations under the Public Health Service Act. These biological products, especially the blood products of human and animal origin, are tested for pyrogenicity; their purity is determined in part by total solids content; and moisture determinations are made as a measure of stability of dried products. The principal products for pyrogen testing, which are submitted by licensed manufacturers for release, include streptokinase-streptodornase, vaccines, antivenins, antitoxins, blood albumin, globulin, fibrinogen, fibrinolysin, plasma and serums.

During the year (November 1, 1961 to November 1, 1962) a total of 1101 samples were tested for pyrogenicity which required the use of approximately 3300 rabbits. This figure includes 605 samples submitted for release, 48 for the Laboratory of Blood and Blood Products, 111 for the NIH Clinical Center Blood Bank, 315 pharmaceutical preparations for the NIH Clinical Center Pharmacy, and 12 samples from the NIH Media Department. Studies were made to determine the test dose in rabbits on pharmaceutical products for which no pyrogen test dose had been established.

All pyrogen test results reported in the manufacturers' protocols to the Laboratory of Control Activities were evaluated. On the basis

of these evaluations and additional DBS tests on samples of the product submitted, recommendations for release or rejection were made. Records of all tests were maintained and officially reported.

Twelve visiting scientists from domestic and foreign health laboratories and from licensed biological establishments were shown the techniques used in performing the work of this section. The chief of this section also assisted in the annual inspection program of several licensed manufacturers and served on a committee to make a recommendation on the suitability of a lot of yellow fever vaccine secondary seed virus proposed for use by a licensed manufacturer. Throughout the year several conferences were held with representatives of licensed biological establishments on problems dealing with the pyrogen test.

Samples of each lot of Normal Human Serum Albumin released by the Laboratory of Control Activities continue to be distributed to different hospitals for clinical testing. Reports received on these lots of albumin confirm the reliability of the pyrogen test as a means of determining the safety of the product.

Work was done on a cooperative study with two licensed manufacturers to check the validity of their pyrogen tests results on seven lots of Fibrinogen and Poliomyelitis Immune Globulin which gave questionable pyrogenic results. Carefully controlled comparative tests in this laboratory confirmed that these seven questionable lots were pyrogenic.

A study was completed to determine whether or not it is necessary to continue the six hour pyrogen test readings on a new product (Fibrinolysin) being developed and coming into clinical use. Comparative hourly test readings on nineteen different lots after three hours and six hours respectively showed that the usual three hour test readings are satisfactory. These findings were confirmed by three licensed manufacturers with comparative tests on a total of 75 different lots.

Control work in this section involves studies designed to adapt the above mentioned tests to new products, to study the factors influencing the test, and the adaptability of these tests as a means of evaluating the safety of experimental pharmaceuticals, including radioactive isotopes, under development by the NIH Pharmacy Department for clinical study in the NIH Clinical Center.

Part B included Yes /__/ No /X/

Serial No. DBS 11
1. Bacterial Products
2. Bacterial Vaccines
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A

Project Title: Pertussis Vaccine

Principal Investigator: Dr. Margaret Pittman

Other Investigators: Mrs. Claire B. Cox, Mrs. Roberta A. Gardner

Cooperating Units: None

Man Years:

Total:	2.7
Professional:	1.2
Other:	1.5

Project Description:

Objectives: The objective is that all lots of products containing pertussis vaccine issued by U. S. licensed establishments have optimum properties: adequate and stable potency throughout the dating period and relative freedom from untoward reactive substances.

Methods Employed: 1. The potency and toxicity of the pertussis vaccine component of all lots of products containing this antigen are kept under surveillance by testing the majority of lots submitted for release (about 200 per year) for potency and freedom-from-toxicity and all inspection samples for potency, by reviewing protocols and license applications and by conferences with technical representatives from manufacturers. 2. Instability of pertussis vaccine in the presence of poliomyelitis vaccine is being investigated by observing the effect of preservatives and various components of poliomyelitis vaccine on the potency of pertussis vaccine, also the effect of enzymes on the bacterial cell wall with which the protective antigen is closely associated. 3. Special study on the adequacy of the revised potency and dating period for pertussis vaccine in quadruple antigen vaccine. 4. Dose-response toxicity tests of each manufacturer's products containing pertussis vaccine to evaluate the adequacy or feasibility of the revised requirements for freedom-from-toxicity.

Major Findings: (1) In general, lots of single or triple antigen vaccines have remained satisfactory in potency, stability

and toxicity. (2) With the use of the revised toxicity test there has been an overall slight reduction in mouse toxicity of vaccines with no apparent decrease in potency.

Significance to bio-medical research and the program of the Division: The surveillance of and research on pertussis vaccine provides information relating to control and improvement of the product and basic scientific information about immunological and reactive properties of Bordetella pertussis.

Proposed Course of Project: Emphasis will be placed on the investigation to determine the cause of instability of potency of pertussis vaccine in the presence of poliomyelitis vaccine. The other parts of the project will be continued as outlined above.

Part B included Yes [X] No [ ]

PHS-NIH
Individual Project Report
Calendar Year 1962

Part B: Honors, Awards, and Publications

Publications other than abstracts from this project.

Pittman, M. Instability of Pertussis-Vaccine Component in Quadruple Antigen Vaccine, JAMA 181: 25-30, 1962.
(Listed as in press in report for calendar year 1961.)

Participated in Round Table Conference on Pertussis Immunization, June 13--16, 1962, Prague, Czechoslovakia. Presented paper entitled "Some factors which influence potency evaluation of pertussis vaccine."

Serial No. DBS 12
1. Bacterial Products
2. Bacterial Vaccines
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A

Project Title: Typhoid Vaccine

Principal Investigator: Dr. Margaret Pittman

Other Investigators: Mr. Howard Bohner
Mr. James F. Marshall

Cooperating Unit: World Health Organization

Man Years:
Total : 0.6
Professional : 0.2
Other : 0.4

Project Description:

The project is a continuation of the one described in the 1961 Report. It was extended at the request of WHO (1) to include assays of additional typhoid vaccines on field trial in Poland and Russia and (2) to obtain additional information on influence of route of vaccination of mouse measured relative potencies.

Objectives: The original objective was for collaborating laboratories to study various methods of potency assay of two typhoid vaccines with the view that one or more assay methods would reflect the relative potencies as determined by field trials. This has been extended to cover other vaccines prepared by different methods.

Methods Employed: The Polish and Russian vaccines have been tested to determine potency relative to K by using the official U.S. potency assay. Further, the influence of subcutaneous and intraperitoneal routes of vaccination on mouse relative potency has been studied using the NIH No. 4 reference vaccine and three of the field trial vaccines which were prepared by different methods--acetone-killed-dried, heat-killed-phenolized and alcohol precipitated.

At the end of 1962, the analyzed results obtained in the collaborating laboratories will be presented by WHO to laboratory

investigators at Geneva for their evaluation in relation to field trial results which show that the acetone-killed-dried vaccine (K) provides significantly better protection to man than the heat-killed-phenolized vaccine (L).

Major Findings: The following results have been obtained in our laboratory: (1) It was reported last year that the Vi, O and H antibody in rabbits to the two vaccines did not differ significantly. (2) In mouse protection tests the relative potencies of K and L were dependent on the route of vaccination:

(a) With subcutaneous vaccination followed by intraperitoneal challenge of culture suspended in saline or mucin there was no significant difference between K and L, although L in each series of tests was better than K.

(b) With intraperitoneal vaccination and mucin challenge, K was significantly better than L. The factor was 3--4 times.

(c) K given intraperitoneally afforded significantly better protection than when given subcutaneously.

(d) L given subcutaneously afforded better protection than when given intraperitoneally but difference was not significant at 5% probability level.

(e) The Russian alcohol vaccine B was equal in potency activity to K by intraperitoneal route. Protection was better by intraperitoneal route than by subcutaneous route.

(f) The NIH reference vaccine No. 4 was significantly less potent than K or L by either route, but was significantly better by subcutaneous than intraperitoneal route.

(g) The Polish acetone-killed vaccine tested only by the intraperitoneal route was equal to K on a bacterial count basis. The other preparations were lower in potency.

(3) ED50 and relative potency values obtained with 7- and 14-day intervals between vaccination and challenge were similar.

Significance to bio-medical research and the program of the Division: Our results and those of a similar nature obtained in collaborating laboratories should have far reaching influence on the method of preparation of typhoid vaccine and the standardization of its potency.

Proposed course of Project: The termination of the project will be dependent on the recommendations of the laboratory workers at Geneva.

The merits of our works for publication will be evaluated; the results will be written up and filed with the Division; and recommendations will be made for a revision in U. S. requirements for typhoid vaccine.

No further experimental work has been planned.

Part B included Yes [ ] No [X]

Serial No. DBS 13
1. Bacterial Products
2. Bacterial Vaccines
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A

Project Title: Investigations Concerning Sterility Testing

Principal Investigator: Mrs. Claire B. Cox

Other Investigators: Dr. John C. Feeley
Dr. Margaret Pittman

Cooperating Units: None

Man Years:
Total: 0.62
Professional: 0.62
Other: none

Project Description:

Objectives: The inclusion of a specific sterility test for fungi in Regulations revealed a lack of published data on which to base definitive procedures. The objects of this study are to re-evaluate the procedures specified for the sterility test with a view to improving the test, not only by providing optimum conditions for the detection of the presence of contaminating bacteria, fungi and yeasts but, also, by simplifying the procedures.

Methods Employed: The methods employed are those usually associated with sterility testing and experiments designed to observe the influence of temperature of incubation on the action of preservatives, length of incubation time, media and the interrelation of these factors on the detection of fungi and yeasts in the presence of biologics (typhoid vaccine and 1.0% plasma).

Major Findings: 1. Length of Incubation Time. For maximum recovery of fungi, 21 days of incubation is required.
2. Media. In the absence of preservatives, fungi and yeasts grew equally well in Fluid Thioglycollate Medium (FTM) as they did in Fluid Sabouraud Medium (FSM). In the presence of Merthiolate, FTM was better than FSM.

3. Preservatives. Under simulated manufacturing storage conditions, Merthiolate exhibited a greater fungicidal activity than phenol.

4. Dual temperature incubation (22° C for 3 days → 30° C for 18 days). Without preservative growth was comparable in FTM and FSM. In presence of Merthiolate, growth occurred in FTM (not in FSM) at 22° C but it was inhibited at 22° → 30° C. Results suggest that at the higher temperature the Merthiolate-HS bond is less stable and Merthiolate becomes available for fungicidal activity. Hence, fungi in product might not be detected with incubation at 22°→ 30° C.

Significance to bio-medical research and the Division: This project is of particular significance to the Division in relation to control of the safety and purity of biological products. Since it is essential that products be free of contaminating microorganisms throughout manufacture, the aim of the present study is to provide more sensitive methods for the detection of fungi and yeasts and at the same time try to simplify the testing procedure.

Proposed Course of Project: Further studies on the anti-microbial activity of other preservatives and means of neutralizing these are contemplated. Studies will be carried out with bacteria to determine whether or not Merthiolate exerts its activity on bacteria growing at 30° C in Fluid Thioglycollate Medium as it does with fungi.

Part B included Yes [X] No [ ]

PHS-NIH
Individual Project Report
Calendar Year 1962

Part B: Honors, Awards, and Publications.

Publications other than abstracts from this project.

Pittman, M. and Feeley, J. C. "Sterility Testing: Detection of fungal and yeast contamination in biological preparations." Proc. 7th International Congress for Microbiological Standardization. Edinburgh (and London), E. & S. Livingstone Ltd., 1962, pp. 207-219. (Listed in 1961 Report as in press.)

Serial No. 14
1. Bacterial Products
2. Bacterial Vaccines
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A

Project Title: Studies on Cholera Vaccine

Principal Investigator: Dr. John C. Feeley

Other Investigator: Dr. Margaret Pittman

Cooperating Units: NIH Cholera Advisory Committee

Man Years:

Total:	0.8
Professional:	0.4
Other:	0.4

Project Description:

Objectives: The establishment of an improved U. S. Standard of Potency for cholera vaccine and formulation of other requirements for this product.

Methods Employed: 1) The quantitative mouse protection test has been employed to accomplish the following:

a) Gain additional data on the potency of representative lots of cholera vaccine prepared by U. S. licensed manufacturers.

b) Assay the protective activity of U. S. cholera vaccines against strains of El Tor vibrios from recent Southeast Asian epidemics of cholera.

2) Data are being accumulated on methods of standardizing the bacterial content of cholera vaccine in terms of opacity, nitrogen content, and direct microscopic and colonial unit counts.

Major Findings: Studies on the relative potency of representative cholera vaccines prepared by the four U. S. licensed firms producing this product have confirmed and extended the earlier impression that wide variations in potency exist for vaccines in current use. Products prepared by a given manufacturer seemed relatively consistent in potency. However, differences in potency between manufacturers were evident with one firm producing vaccine considerably less potent than

the reference vaccines and another firm producing a product that was considerably more potent. The remaining two firms produced vaccines of potency approximately equal to the reference preparations.

Additional studies on mouse protective activity of current cholera vaccines against El Tor vibrios have confirmed the previously reported impression that protection was equally as good as against classic cholera vibrios. It is felt that previous reports to the contrary could best be explained by the use of toxic challenge doses. These findings have been described in a paper accepted for publication in the Bulletin of the World Health Organization.

Data available at the present time suggest that there is some relationship between antigen content and total nitrogen. However, it is recognized that this relationship may vary with the manufacturing process employed and will be invalid in those cases in which the cultures are grown in liquid media when both media and bacteria are incorporated into the vaccine.

Significance to bio-medical research and the program of the Division: The quantitative mouse protection test will provide a method for more precise evaluation of the potency of cholera vaccine. The relationship of mouse measured potency to prophylactic value in humans is not known. Field trials contemplated by WHO and the Pakistan-SEATO Cholera Research Laboratory may provide this information; the vaccines employed will be tested by the mouse protection procedure and other methods to establish a meaningful standard of potency.

Cholera vaccine is generally regarded as one of the more reactigenic of the immunizing agents used in man. There are no specific requirements for toxicity and bacteria content determinations have been inadequate. The physical and chemical data such as nitrogen content and dry weight should be of assistance in controlling the bacterial content thereby reducing the incidence of untoward reactions to the vaccine.

Proposed Course of Project: To carry through as indicated above. On the strength of presently available data, a revision in Minimum Requirements: Cholera Vaccine will be proposed. A manuscript describing the mouse protection test is in preparation and will be submitted for publication.

Part B included Yes [X] No [ ]

PHS-NIH
Individual Project Report
Calendar Year 1962

Part B: Honors, Awards, and Publications

Publications:

Pittman, M. and Feeley, J. C. Protective activity of cholera vaccines against El Tor cholera vibrios. Bull. Wld. Hlth. Org. (In press.)

Feeley, J. C. and Pittman, M. A mouse protection test for assay of cholera vaccine. Proceedings of SEATO Conference on Cholera, Dacca, East Pakistan, Dec. 5--8, 1960. Bangkok, 1962, p. 92. (Previously reported in 1960 Annual Report.)

Serial No. DBS 15
1. Bacterial Products
2. Bacterial Vaccines
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A

Project Title: Serologic Studies on Cholera

Principal Investigator: Dr. John C. Feeley

Other Investigator: Dr. O. Ross McIntyre
Mr. Roland E. Mills

Cooperating Units: NIH Cholera Advisory Committee
Pakistan-SEATO Cholera Research Laboratory

Man Years:

Total:	0.50
Professional:	0.25
Other:	0.25

Project Description:

Objectives: To study the antibody response to acute infection of Vibrio comma (El Tor biotype) and to relate the findings to antibody status of healthy subjects in endemic and non-endemic areas. This project is a continuation of serologic studies begun during the Philippine epidemic of 1961.

Methods Employed: Three serologic techniques were employed: (1) the agglutination test of Goodner et al using living vibrios, (2) a vibriocidal test method based on the broth assay of Muschel and Treffers, and (3) a neutralization test designed to measure antibody to the El Tor vibrio hemolysin.

Paired acute and convalescent phase serum specimens were obtained from patients during the 1961 Philippine epidemic of El Tor cholera. Also examined were sera from presumably healthy Filipinos, Americans, and Pakistanis. The latter sera were submitted by the Pakistan-SEATO Cholera Research Laboratory.

Major Findings: A four-fold or greater rise in antibody, adequate for serologic diagnosis of the disease, was obtained on 91 percent of the patients by agglutination and 94 percent by the vibriocidal method. Sixty percent showed a four-fold or greater rise by the hemolysin neutralization

procedure. The latter provides evidence that the hemolysin is elaborated during growth of the El Tor vibrio in the intestinal tract of man. The agglutination and vibriocidal methods appear to be of approximately equal diagnostic value with paired sera, although the latter is a considerably more sensitive method of measuring cholera antibody.

Studies by the vibriocidal method on "normal" sera revealed measurable levels of antibody in the majority of cases, occasionally at very high levels. The mean vibriocidal titers and range of values encountered were similar for sera from all three countries. Agglutinins were undetectable in most normal sera, but a few had low to moderately elevated titers by this less sensitive method. Only 7 out of 100 normal sera tested were found to have hemolysin-neutralizing antibody. Of particular interest with the Pakistani sera (on which immunization histories are available) is the observation that there was no difference in antibody level in immunized and non-immunized subjects.

Significance to bio-medical research and the program of the Division: The present study confirms the fact that cholera can be diagnosed by serologic methods. Even though less sensitive than the vibriocidal test, the simpler agglutination test is adequate when paired sera are used. On the other hand, the more sensitive vibriocidal test reveals antibodies in the vast majority of normal sera and in titers which, surprisingly enough, do not differ significantly regardless of whether or not the individual is likely to have been exposed to cholera. The origin of these and other "naturally-occurring" antibodies is one of immunology's most intriguing problems. Studies of this type provide important background information relative to the problem of immuno-prophylaxis of cholera.

Proposed course of Project: When the opportunity arises, it is hoped that these methods can be employed to measure the immunologic response of human subjects to cholera immunization and eventually correlated with actual immunity. A manuscript describing the findings to date is in preparation.

Part B included Yes / / No /x/

Experiments using the tube hemolysis procedure with blood cells from species other than sheep indicated that erythrocytes from man, horse, cow, rabbit, guinea pig, and mouse could also be employed for identification of the El Tor vibrio. Contrary to the literature, no evidence of hemolytic activity of classic cholera vibrios for human erythrocytes was obtained. Chicken erythrocytes were not readily lysed by most El Tor strains but were regularly hemagglutinated.

Comparative studies indicated, also contrary to the literature, that hemolytic activity of El Tor vibrios could be readily detected on sheep blood agar plates, provided that only hemolytic zones surrounding well isolated colonies were considered. No such zones were observed around isolated colonies of classic cholera strains, but apparent hemolysis ("hemodigestion") was present in areas of confluent growth. The latter phenomenon appears to be due to low molecular weight alkaline metabolic products, which unlike the specific El Tor hemolysin, are diffusable through dialysis membranes. Human and rabbit blood agar plates were unsatisfactory probably due to greater sensitivity to lysis by the low molecular weight components. Weak zones of hemolysis occurred even around isolated colonies.

Significance to bio-medical research and the program of the Division: This study supports the continued use of hemolytic activity as the principal criterion for identification of the El Tor biotype of V. comma. Recent studies have often favored the use of other less-documented methods (e.g. phage typing) instead of hemolysis. With improved precision in detection, hemolytic activity is more valuable than ever as a bacteriologic tool in the characterization of strains in epidemiological studies.

Proposed course of Project: Further work in this area is not contemplated at this time. A manuscript describing the work done subsequent to the first paper now in press is being prepared.

Part B included Yes / x / No / /

PHS-NIH
Individual Project Report
Calendar Year 1962

Part B: Honors, Awards, and Publications

Publications other than abstracts from this project:

Feeley, J. C. and Pittman, M. Studies on the hemolytic activity of Vibrio comma, El Tor biotype. Bull. Wld. Hlth. Org. (In Press.)

Serial No. DBS 17
1. Bacterial Products
2. Bacterial Vaccines
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A

Project Title: Experimental Cholera Studies in the Folic Acid Depleted Mouse

Principal Investigator: Dr. O. Ross McIntyre

Other Investigator: Dr. John C. Feeley

Cooperating Unit: Pakistan SEATO Cholera Research Laboratory, Dacca, East Pakistan

Man Years:

Total:	0.08
Professional:	0.04
Other:	0.04

Project Description:

Objectives: It has recently been suggested that susceptibility to cholera infection may be determined by a pre-existing chronic enteritis. This theory is based on a biopsy study of the small bowel by Gangarosa. The observation that folic acid treatment reverses some of the features of the chronic enteritis in tropical sprue has suggested the present study, the object of which is to determine if folic acid deficient animals are susceptible to infection by Vibrio comma, and if so to determine if this is a practical means of producing an experimental model for the study of cholera infection in laboratory animals.

Methods Employed: Folic acid deficiency will be produced in laboratory rodents by administering sulfonamides in a diet deficient in the vitamin. The administration of antifolic acid compounds such as methotrexate will also be used as a means of inducing deficiency. Toxicity will be followed and quantitated by weight curves for the experimental and control groups, time of onset and degree of leukopenia and anemia, and the time of onset of diarrhea.

Strains of V. cholera will be administered at several stages of vitamin deficiency after stopping the administration of the antibacterial drug in the diet. If these efforts fail, the deficient animals will be given a streptomycin resistant strain of V. comma which has been

demonstrated previously by Dr. John Feeley to produce an assymptomatic infection in mice when given concomitantly with streptomycin. It will be determined whether the experimental animals develop fatal diarrhea with a multiplication of the infecting organism.

Major Findings: None to date.

Significance to bio-medical research and the program of the Division: The study may possibly provide a suitable experimental model as well as contribute to the understanding of what conditions predispose to human infection.

Proposed course of Project: To proceed as outlined above.

Part B included Yes / / No / x /

Serial No. DBS 18
1. Bacterial Products
2. Bacterial Vaccines
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A

Project Title: Isolation of Cholera Vibrios by Positive Recognition Plating Procedures

Principal Investigator: Dr. John C. Feeley

Other Investigator: None

Cooperating Unit: Pakistan-SEATO Cholera Research Laboratory

Man Years:

Total:	0.02
Professional:	0.02
Other:	0.0

Project Description:

Objectives: To determine the relative value of the stereomicroscopic-oblique light and gelatinase-zone procedures for recognition of colonies of Vibrio comma on agar plates inoculated with cholera stool specimens.

Methods Employed: Stool specimens from cholera patients and contacts collected by the investigator during a visit at the Pakistan-SEATO Cholera Research Laboratory in Dacca were plated on various media. Methods employed for recognition of cholera vibrios are described in the publication listed in Part B.

Major Findings: Both methods under investigation were excellent and of approximately equal value in the isolation of V. comma. The study provides additional evidence of the value of simple non-inhibitory culture media for isolation of V. comma. The two methods may be combined for even greater efficiency.

Significance to bio-medical research and the program of the Division: The use of these methods greatly simplifies the isolation of cholera vibrios from stool specimens.

Proposed Course of the Project: Further work on this project is not contemplated.

Part B included Yes [X] No [ ]

PHS-NIH
Individual Project Report
Calendar Year 1962

Part B: Honors, Awards, and Publications

Publications other than abstracts from this project:

Feeley, J. C. Isolation of cholera vibrios by positive-recognition plating procedures. J. Bacteriol. 84: 866-867, 1962.

Serial No. DBS 19
1. Bacterial Products
2. Bacterial Vaccines
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A

Project Title: Studies on Genetic Transformation of Vibrio comma

Principal Investigator: Dr. John C. Feeley

Other Investigator: Mr. Estill L. Caudill

Cooperating Units: None

Man Years:

Total:	0.35
Professional:	0.25
Other:	0.1

Project Description:

Objectives: The principal objective of the present work was to investigate the susceptibility of various strains of Vibrio comma to DNA mediated genetic transformation.

Methods Employed: In general, the methods employed were similar to those which have proved successful in the transformation of other bacteria (e.g. Haemophilus influenzae and Diplococcus pneumoniae). Crude and purified preparations of DNA obtained from one-step streptomycin resistant mutants were tested for transforming activity of the streptomycin-resistance marker upon streptomycin sensitive cells of the same and other strains.

Major Findings: Despite a number of trials and variations in experimental procedure, no evidence of successful genetic transformation was obtained. It may be that the proper conditions were not provided. Accordingly, the possibility of transformation cannot be ruled out entirely.

Significance to bio-medical research and the program of the Division: The existence of a DNA-mediated genetic exchange mechanism in V. comma would be of interest in regard to the intriguing questions centering around the possibility of transformations of nonagglutinable (NAG) vibrios to agglutinable vibrios, of Ogawa serotype to Inaba serotype, and classic cholera (nonhemolytic) strains into El Tor strains (hemolytic).

Serial No. DBS 20
1. Bacterial Products
2. Bacterial Vaccines
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A

Project Title: Determination of Serum Antibody Levels against Vibrio comma and so-called "NAG" Vibrios in Non-Immunized Americans

Principal Investigator: Dr. O. Ross McIntyre

Other Investigator: Dr. John C. Feeley

Cooperating Unit: Pakistan SEATO Cholera Research Laboratory, Dacca, East Pakistan

Man Years:

Total:	0.08
Professional:	0.04
Other:	0.04

Project Description:

Objectives: The objectives of this project will be to document the level of antibodies to Vibrio comma and "NAG's" in American individuals who have not been previously immunized with cholera vaccine and to compare the observed titers with those obtained on individuals in the endemic cholera area.

Methods Employed: Agglutinating antibody levels will be determined by the tube method recommended by Dr. Kenneth Goodner and bacteriocidal antibodies by the method of Dr. John Feeley.

Major Findings: None to date.

Significance to bio-medical research and the program of the Division: 1) Elevated antibodies against vibrios, if demonstrated in Americans, would indicate prior infection with these or similar antigens. The means and mechanism of infection would then necessarily have to be defined. Though it is held unlikely at the moment, the concept that certain unexplained cases of diarrhea in this country result from infection with NAG's would be strongly supported by such a demonstration, and should lead to efforts to isolate the bacteria in such instances. 2) If antibodies to these bacteria are not found, it would indicate that humans in the United States are not infected by these agents although they have been exposed to them. The reasons for this would then require

exploration. 3) The results of this study would add perspective to the study of serological immunity to vibrios among Pakistanis which is being carried out by the Pakistan SEATO Cholera Research Laboratory. Further, it would add to the understanding of what part serological immunity plays in the prevention of diarrheal disease caused by vibrios.

Proposed Course of Project: Collection of the sera and vibrios to be used will be followed by study using the methods outlined above.

Part B included Yes / / No /X/

Serial No. DBS 21
1. Bacterial Products
2. Allergenic Products
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A

Project Title: Studies on the Specificity of Tuberculin

Principal Investigators: Dr. Harold Baer
Dr. Sotiros D. Chaparas

Other Investigators: Dr. Caspar W. Hiatt (LBB)
Mr. Raoul J. Benoit (LBB)

Cooperating Units: Laboratory of Biophysics and Biochemistry

Man Years:

Total:	2.1
Professional:	1.0
Other:	1.1

Project Description:

Objectives: The purpose of this project is to ascertain whether it is possible to prepare a tuberculin with greater specificity than those currently available.

Methods Employed: Culture filtrates and bacterial autolysates of the BCG strain of Mycobacterium tuberculosis are being fractionated and analyzed chemically and immunochemically to determine whether some fractions of this complex material are more specific than others. Guinea pigs sensitized to several species of mycobacteria, respectively, are being employed to determine the specificity of the tuberculin fractions.

Major Findings: Different antigenic substances have been found in BCG culture filtrates and autolysates as well as in various commercially obtained PPD preparations. Many of the fractions prepared from these materials exhibit skin reactivity in sensitized guinea pigs. One of these fractions is almost completely polysaccharide while the others are largely protein in nature. The polysaccharide material seems to exhibit most of the specificity of these fractions. It reacts most strongly in homologously sensitized guinea pigs and weakly in guinea pigs sensitized with other mycobacteria. All of the fractions seem to have from 4 to 8 components when analyzed by agar diffusion using rabbit antisera. It, therefore, would seem possible to increase the specificity of polysaccharide

fractions by further fractionation to isolate a more purified fraction which is responsible for the skin reactivity. Since a polysaccharide fraction as well as protein fractions is skin reactive in sensitized guinea pigs, it appears to be definite that there is more than one substance which can elicit the tuberculin reaction.

Significance to bio-medical research and the program of the Division: The isolation of purified substances that produce the typical tuberculin reaction in appropriately sensitized animals may result in more reliable, specific, and reproducible standards.

Proposed course of Project: Continued efforts toward further purification and characterization of the fractions and analyses of the newer fractions for skin reactivity and specificity in eliciting the tuberculin reactions.

Part B included Yes / / No / x /

Serial No. DBS 22
1. Bacterial Products
2. Allergenic Products
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A

Project Title: Standardization of Poison Ivy Extracts

Principal Investigator: Dr. Harold Baer

Other Investigator: Mr. Robert Bowser

Cooperating Units: None

Man Years:

Total:	1.5
Professional:	0.5
Other:	1.0

Project Description:

Objectives: (1) Investigate the feasibility of producing a standard of potency for poison ivy extracts. (2) Study the immunology of poison ivy extracts and one of its components, 3-pentadecylcatechol (PDC).

Methods Employed: Guinea pigs are made sensitive with PDC or poison ivy extract and then skin tested as described in the 1961 Annual Report. Studies are continuing on the passive transfer of this sensitivity by lymph node cells from sensitized animals to normal animals. A study has also been made of the effect of the age of guinea pigs on their ability to become sensitized.

Major Findings: Guinea pigs injected with either PDC or poison ivy extract react to both substances. It is possible to titrate this sensitivity in a reproducible fashion. By using PDC as a standard it was found possible to assay various poison ivy extracts for their content of active material. By sensitizing animals at ages varying from 2 months to 3 years it was found that the younger animals can be made more sensitive than the older animals. It has been found that injection of PDC prior to its injection with complete adjuvant prevents the development of typical delayed contact sensitivity.

The typical sensitivity can be transferred from sensitive to normal strain 13 guinea pigs by means of lymph node cells. The duration of this passive transfer has been found to be greater than 3 months.

Significance to bio-medical research and the program of the Division: In this project attempts are being made to learn about the basic immunological phenomena associated with poison ivy sensitivity. It should be possible, eventually, to determine the composition and concentration of ingredients in extracts used for skin testing and desensitization.

Proposed course of Project: Studies will be continued on the immunology of poison ivy sensitivity and the relationship of the human disease to the phenomena observed in guinea pigs.

Part B included Yes / / No /x/

Serial No. DBS 23
1. Bacterial Products
2. Allergenic Products
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A

Project Title: Gas Chromatographic Analyses of the Poison Ivy Extracts

Principal Investigators: Dr. Harold Baer
Dr. Arthur Karmen (LTD, NHI)

Other Investigators: Mr. Robert T. Bowser
Dr. Swamy Srinivasan (LTD, NHI)

Cooperating Unit: Laboratory of Technical Development, NHI

Man Years:
Total: 0.2
Professional: 0.2
Other: 0.0

Project Description:

Objectives: To investigate the use of gas chromatography to analyze poison ivy extracts for the individual catechols and to compare the concentration of catechols so obtained with the reactivity of these substances in sensitized guinea pigs.

Methods Employed: Pentadecylcatechol (PDC) had to be acetylated prior to gas chromatography in order to obtain a peak that emerged at a reproducible time. The poison ivy extracts, therefore, had to be acetylated prior to analyses. Guinea pigs sensitized to PDC were simultaneously tested with PDC and poison ivy extracts in order to make a direct comparison of these substances for their ability to elicit reactions.

Major Findings: Following acetylation of an extract that was reactive in guinea pigs, 3 peaks were found that corresponded to PDC and its unsaturated derivatives. The concentration of these materials obtained from the area under the peaks was almost identical with the concentration of the catechols as measured in sensitized guinea pigs with PDC as standard. It, therefore, appears that the total activity of poison ivy extracts is associated with the catechol content and that the guinea pig assay should be suitable for this purpose. Those extracts which produce no peaks in the gas chromatograph were devoid of activity when tested in guinea pigs.

Significance to bio-medical research and the program of the Division: It is now possible to assay poison ivy extracts for their total concentration of catechols by means of a guinea pig assay and for the individual catechols by the gas chromatographic assay. A laboratory test is, therefore, available to determine the potency of products and to relate this potency to a physical standard, i.e., synthetic PDC.

Proposed course for Project: No further work with gas chromatography is immediately contemplated. Since the guinea pig assay appears to be satisfactory, future work will be concentrated on this procedure.

Part B included Yes /x/ No /___/

PHS-NIH
Individual Project Report
Calendar Year 1962

Part B: Honors, Awards, and Publications

Publications other than abstracts from this project:

Srinivasan, S., Baer, H., Bowser, R. and Karmen, A. An Assay for Pentadecylcatechols in Poison Ivy Extracts by Gas Chromatography. Anal. Biochem. (In Press)

Serial No. DBS 24
1. Bacterial Products
2. Allergenic Products
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A

Project Title: Studies on the Serum Proteins, Skin Reactivity and Pathology of Animals Injected with Freund's Adjuvants

Principal Investigators: Dr. Sotiros D. Chaparas
Dr. Harold Baer
Dr. Edwin M. Lerner (LGFAR, NIAID)

Other Investigators: Mr. Robert T. Bowser
Dr. Stewart Sell (LGFAR, NIAID)

Cooperating Unit: Laboratory of Germfree Animal Research, NIAID

Man Years:

Total:	0.2
Professional:	0.2
Other:	0.0

Project Description:

Objectives: To determine some of the effects of mineral oil adjuvants on guinea pigs.

Methods Employed: Guinea pigs, both normal and germfree, have been injected with mineral oil emulsions with and without mycobacteria. Serum from these animals has been examined by paper and immunoelectrophoresis for changes in the protein concentration and content. Some studies have also been made on the antibody response in the animals that received protein antigens in addition to mycobacteria.

Major Findings: The major changes as outlined in the 1960 Report occurred in the gamma globulin content of the sera. In the serum of some of the germfree guinea pigs injected at an early age a new protein was found. The new protein which was detected by immunoelectrophoresis does not seem to be present in sera of normal guinea pigs.

Significance to bio-medical research and the program of the Division: Since oil emulsions have been used experimentally in adjuvant preparations for vaccines and for the treatment of allergies and are being considered for general use, it is important to determine whether these substances have any affects on animals.

Proposed course of Project: Determine the nature of the newly observed component in germfree animals and the conditions under which it arises.

Part B included Yes / / No /x/

Serial No. DBS 25
1. Bacterial Products
2. Allergenic Products
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A

Project Title: Blood Group A,B,O(H) Activity of Urine

Principal Investigators: Dr. Harold Baer
Dr. Allan Kliman

Other Investigators: None

Cooperating Units: None

Man Years:
Total: None
Professional: None
Other: None

Project Description:

This project has been terminated. A publication for this project is given in Part B.

Part B included Yes / x / No / /

PHS-NIH
Individual Project Report
Calendar Year 1962

Part B: Honors, Awards, and Publications

Publications other than abstracts from this project:

Baer, H. and Kliman, A. Blood Group A,B,O(H) Activity of Urine. Proc. Soc. Exp. Biol. and Med. 111(4):702, August-September 1962.

Serial No. DBS 26
1. Bacterial Products
2. Bacterial Toxins
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A

Project Title: The Schick Test Toxin (Diphtheria)

Principal Investigator: Dr. Michael F. Barile

Other Investigators: Mr. Donald B. Riggs
Mr. Robert W. Kolb (LCA)

Cooperating Unit: Laboratory of Control Activities, DBS

Man Years:

Total:	0.1
Professional:	0.1
Other:	0.0

Project Description:

Experimental work as given in the 1961 Report has been completed. A report of findings and a draft of proposed specifications (Additional Standards) for the product have been prepared and submitted for DBS' consideration.

Significance to bio-medical research and the program of the of the Division: The present study will provide background information for the re-evaluation of the present requirements and a revision of standards for Diphtheria Toxin for the Schick Test.

Proposed course of Project: The proposed potency assay and Standard Diphtheria Toxin for the Schick test will be submitted to the manufacturer for comment and a report of studies prepared for publication.

Part B included Yes / / No /X/

Serial No. DBS 27
1. Bacterial Products
2. Bacterial Toxins
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A

Project Title: Investigation of Tetanus Toxoids for Prevention of Neonatorum Tetanus

Principal Investigator: Dr. Margaret Pittman

Other Investigators: Dr. Michael F. Barile
Dr. M. Carolyn Hardegree
Dr. Edward B. Seligmann, Jr., LCA
Dr. Frank Schofield

Cooperating Units: Department of Public Health, Territory of Papua and New Guinea
Laboratory of Control Activities, DBS

Man Years:

Total:	2.4
Professional:	1.2
Other:	1.2

Project Description:

Objectives: Neonatorum tetanus is an important cause of infant mortality in a number of areas in the world. Prevention by means of vaccination of pregnant women is under investigation in New Guinea. The main objective of the LBP part of the project is to correlate laboratory assays of experimental tetanus toxoids with field trial response and to relate the results to U. S. reference tetanus toxoids (tested concurrently in animals) and the requirements for this product.

Methods Employed: 1) Active mouse potency assays of the toxoids; 2) guinea pig potency assays by titrating antitoxic response by means of animal neutralization and in vitro hemagglutination tests; 3) titration of antitoxic response of human subjects by means of mouse neutralization and hemagglutination tests.

Major Findings: Preliminary work on experimental procedures is nearing completion. The results follow: 1) Tests confirmed previous reports that tissue cell culture and in vivo dermal cells were not responsive to tetanus toxin. 2) More consistent results were obtained following subcutaneous than intraperitoneal route of immunization.

3) A suitable toxin and proposed U. S. reference toxoids (plain and alum precipitated) have been selected. The major investigation is in the initial stage.

Significance to bio-medical research and the program of the Division: Information will be obtained concerning the relative value of various quantitative methods of titrating tetanus toxoids and antitoxin which might be applicable to the improvement of the present official tests.

Proposed Course of Project: To proceed as outlined above.

Part B included Yes [ ] No [X]

Serial No. DBS 28
1. Bacterial Products
2. Bacterial Toxins
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A

Project Title: A Study of the Antigenic Products of Various Strains of Clostridium tetani

Principal Investigator: Dr. M. Carolyn Hardegree

Other Investigators: None

Cooperating Units: None

Man Years:

Total:	5/12
Professional:	2.5/12
Other:	2.5/12

Project Description:

Objectives: 1. To determine the antigens present in culture filtrates of different strains of Cl. tetani. 2. To separate the antigens present in the filtrates; in particular, neurotoxin from hemolysin. 3. To study the relationship of these antigens to optimal anti-tetanus immunization.

Methods Employed: 1. Gel diffusion techniques. 2. Immunoelectrophoresis. 3. Zone electrophoresis. 4. Animal bioassay, neutralization and immunization studies. 5. Hemolysin and flocculation determination.

Major Findings: Project not in progress long enough to state major findings.

Significance to bio-medical research and the program of the Division: Purified tetanal neurotoxin may not provide optimal protection against tetanus and other antigenic components of the organism may be important in the immunity produced. It is necessary to know the identity of these antigens and to have them isolated before their role in immunization can be determined. The investigator believes these studies may help explain some of the questions that exist regarding antitoxin unitage titration, flocculation

zones, etc. These questions are relevant to the functions of the Division.

Proposed course of Project: In addition to the methods listed above, column chromatography will be used in attempts to separate neurotoxin from hemolysin and to isolate the protease and histidinase of this organism. Immunization in animals with the products obtained are planned.

Part B included Yes / / No /X/

Serial No. DBS 29
1. Bacterial Products
2. Bacterial Toxins
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A

Project Title: Pleuropneumonia-like Organisms

Principal Investigator: Dr. Michael F. Barile

Other Investigators: Mr. Donald B. Riggs
Dr. Casper W. Hiatt (LBB)
Dr. Robert M. Chanock (LID, NIAID)
Dr. Leon Sokoloff (LEP, NIAMD)

Cooperating Units: Laboratory of Biophysics and Biochemistry, DBS
Laboratory of Infectious Diseases, NIAID
Laboratory of Experimental Pathology, NIAMD

Man Years:

Total:	0.2
Professional:	0.1
Other:	0.1

Project Description:

Objectives: 1) To develop new methods or improve existing methods for detection of PPLO in cell cultures and biological products. 2) To develop methods for elimination of PPLO from cell cultures and biological products. 3) To examine the role of PPLO in infectious diseases of man and animals.

Methods Employed: 1) The fluorescent antibody procedure was developed as a new method of detecting PPLO in contaminated cell cultures. 2) The photodynamic inactivation procedure was examined as a method to eliminate PPLO from cell cultures. 3) The role of PPLO as the causative agent of primary atypical pneumonia in man and obstructive genitourinary disease in mice was examined.

Major Findings: 1) The fluorescent antibody procedure developed for detection of PPLO in contaminated cell cultures has been published as shown in Part B. 2) The photodynamic procedure was found an effective method of inactivating PPLO in suspension and that the degree of susceptibility to this action varied with the PPLO strains tested. 3) The growth on artificial media of an agent

associated with atypical pneumonia and its identification as a PPLO has been reported. Ten patients with primary atypical pneumonia who developed an antibody rise for the Eaton-agent when tested by the classic Eaton-infected chick embryo section technique showed similar results when PPLO colonies from agar media were tested by the immunofluorescent procedure. Since the PPLO agent was antigenically similar to the Eaton egg-propagated agent which is known to cause atypical pneumonia in human volunteers it is implied that the Eaton agent is a PPLO. The Eaton agent PPLO was antigenically distinct from three human oral and four human genital strains of PPLO as well as PPLO strains derived from cows, rats, birds, savage and various tissue culture cell lines. 4) Three forms of obstructive uropathy were found in the majority of male STR/IN mice. Although microorganisms, but not PPLO, were consistently found in association with one form: cystolithiasis, it was not certain whether they were the cause or result of the urinary status. The lesions were under genetic control.

Significance to bio-medical research and the program of the Division: In view of the requirements for determining the presence of PPLO in new products, such as measles vaccine, these studies will provide information for establishing standards for these products.

Proposed Course of Project: To pursue studies to improve methods for the elimination and detection of PPLO in biological products.

Part B included Yes [x] No [ ]

PHS-NIH
Individual Project Report
Calendar Year 1962

Part B: Honors, Awards, and Publications

Publications other than abstracts from this project:

Chanock, R. M., Hayflick, L. and Barile, M. F. Growth on Artificial Medium of an Agent Causing Atypical Pneumonia and Its Identification as a PPLO. Proc. Nat. Acad. Sci. 48: 41-49, 1962.

Barile, M. F. Discussion: Detection and Elimination of Contaminating Organisms. J. Nat. Cancer Institute, Monograph Series # 7, April 1962. (Listed in 1961 Report as in press.)

Barile, M. F. Cultivation of Pleuropneumonia-like Organisms on Membrane disc for Microscopic Examination. J. Bacteriol. 83: 430-432, 1962. (Listed in 1961 Report as in press.)

Barile, M. F., Malizia, W. F. and Riggs, D. Incidence and Detection of Pleuropneumonia-like Organisms in Cell Culture by Fluorescent Antibody and Cultural Procedures. J. Bacteriol. 84: 130-136, 1962.

Sokoloff, L. and Barile, M. F. Obstructive Genitourinary Disease in Male STR/IN Mice. J. Path. 41: 233-246, 1962.

Serial No. DBS 30
1. Viral Immunology
2. Section on Pathology
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A

Project Title : Neurovirulence Tests on Live Poliovirus Vaccines in Monkeys.

Principal Investigator: Dr. Ruth L. Kirschstein

Other Investigators : Dr. Gerald S. Borman, Mr. Ronald Clark, Mr. George Rusten

Cooperating Units : Serology Section screens monkey serums for freedom from antibody to poliovirus

Man Years:

Total	:	15.0
Professional	:	0.5
Other	:	14.5

Project Description:

Objectives: To test Live Poliovirus vaccines for ability to induce poliomyelitis in Rhesus monkeys when inoculated directly into the central nervous system.

Methods Employed: Monkeys were inoculated with vaccine or dilutions thereof either intraspinally or intrathalamically, and observed for evidence of developing paralysis over a period of 17 - 18 days. The monkeys were then sacrificed and the central nervous system examined histologically for evidence of poliomyelitis. In addition tissues were saved for virus isolation attempts. This testing is performed as outlined by the PHS regulations for the Live Poliovirus Vaccines and test results were compared with similar results obtained with the reference vaccine preparations.

Major Findings: The Reference Vaccine has been tested on six separate occasions during 1962 and certain standards have thus been set. A total of 80 vaccine lots have been tested, the testing at present being performed on most of the vaccines submitted. In addition, certain seed virus lots have been tested. A total of 3590 monkeys have been used in this testing. Of the lots tested, 27 have been Type I, 11 have been Type II and 42 have been Type III.

-continued-

On the basis of the findings of these tests, Type III Live Poliovirus Vaccine, Oral, has been licensed by the Government in 1962 and a close check is underway. Evaluation of the qualitative differences seen in monkeys after Type III vaccine is under way.

Significance to the Program of the Division: Integral part of the DBS program of control of Poliovirus Vaccine, Live, Oral.

Proposed Course: This endeavor will continue in 1963 on the same scale.

Part B included yes/ / no/x/

Serial No. DBS 31
1. Viral Immunology
2. Section on Pathology
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A

Project Title : Neurovirulence Tests on Measles Virus Vaccines in Monkeys

Principal Investigator: Dr. Ruth L. Kirschstein

Other Investigators : Mr. Ronald Clark, Mr. George Rusten

Cooperating Units : None

Man Years:

Total	:	2.0
Professional	:	0.1
Other	:	1.9

Project Description:

Objectives: To test Measles Virus Vaccines for the presence of neurotropic agents.

Methods Employed: Monkeys were inoculated as outlined in the proposed PHS regulations for the above vaccines.

Major Findings: Four measles virus vaccines have been tested in 80 monkeys. No evidence of neurotropic agents has been found.

Significance to the Program of the Division: Integral part of the DBS program of the control of viral vaccines.

Proposed Course: It is expected that this endeavor will greatly increase in 1963.

Part B included yes / / no /X/

Serial No. DBS 32
1. Viral Immunology
2. Section on Pathology
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A

Project Title : The Pathogenesis of Infectious Diseases.

Principal Investigator: Dr. Ruth L. Kirschstein

Other Investigators : Dr. Alan Rabson, NCI
Dr. Gregory O'Conor, NCI
Dr. Richard Malmgren, NCI
Dr. Harry Meyer, LVR, DBS
Dr. K. K. Takemoto, NIAID
Dr. Robert Friedman, LVI, DBS
Dr. Paul Gerber, LVI, DBS
Dr. Harold Baer, LBP, DBS
Dr. Sotiros Chaparas, LBP, DBS

Cooperating Units : Laboratory of Virology and Rickettsiology, DBS
Laboratory of Bacterial Products, DBS
Laboratory of Pathology, NCI
Laboratory of Biology of Viruses, NIAID
Pathologic Anatomy Branch, NCI

Man Years:

Total	2.0
Professional	0.2
Other	1.2

Project Description:

Objectives: To study the pathogenesis of various experimental infectious diseases.

Methods Employed: Gross autopsies and histologic examinations were carried out on animals infected experimentally.

Major Findings:

1. (With Drs. Rabson and Gerber) The pathology of the intracranial malignancies produced in hamsters by polyoma and related viruses is being studied in detail. The pathogenesis of these lesions is being studied in detail at the present time.

Studies of the oncogenic properties of a new simian virus (SV-40) revealed that subcutaneous inoculation into newborn hamsters gives rise to subcutaneous fibrosarcomas whereas intracerebral inoculation gives rise to true gliomas of the brain. These gliomas have been found to be ependymomas. The pathogenesis of the disease and interrelationships between the virus and the tumor is being studied in detail at the present time.

2. (With Drs. Rabson and O'Conor) Further studies of the oncogenic properties of SV-40 revealed that it is capable of producing ependymomas in the brains of Mastomys even after subcutaneous inoculation.

3. (With Drs. Kilham and Rabson) Studies on a naturally occurring rat virus and its effect when inoculated into Mastomys have shown that infection with production of inclusion bodies does occur in these animals.

4. (With Drs. Rabson, O'Conor and Malmgren) Studies of the ability of SV-40 to "transform" normal human cell cultures revealed that the resulting cultures have a rapid rate of multiplication. These cultures are carrier cultures for the virus and these transformed cells have the capacity for limited growth as a tumor in the brains of monkeys.

5. (With Dr. Robert Friedman)

a. Studies of the genetic and neurovirulence characteristics of the Sabin Type I live poliovirus vaccine after gastrointestinal passage have indicated that the virus is excreted for prolonged periods of time (up to 120 days) and that, at least, in some individuals, there is a change of the neurovirulence characteristics toward increased virulence. However, the temperature marker,(said to correlate with neurovirulence) did not always show changes.

b. Studies of wild poliovirus strains isolated from paralytic cases reveal that all these viruses are quite virulent for the monkey even though the temperature marker varies considerably.

6. (With Dr. Takemoto) Studies on the neurovirulence for monkeys of plaque variants of attenuated polioviruses are in progress.

7. (With Drs. Baer and Chaparas) Studies of the histologic changes induced by complete and incomplete Freund's adjuvant in guinea pigs and monkeys are in progress.

8. (With Dr. Meyer) Studies on the neurotropic activity of SV-40 and virulent measles viruses are underway.

Part B included yes /X/ no / /

Part B

Honors, Awards and Publications.

1. Gerber, Paul and Kirschstein, R. L.; SV-40 Induced Ependymomas in Newborn Hamsters: I. Virus-tumor Relationships. Virology, Dec.(1962)

2. Kirschstein, R. L. and Gerber, P.; Ependymomas produced after intracerebral inoculation of SV-40 into newborn hamsters. Nature, London. 195: 299-300 (1962)

3. Rabson, A. S., O'Conor, G. T., Kirschstein, R. L. and Branigan, W. J.; Papillary Ependymomas Produced in Rattus (Mastomys) Natalensis Inoculated with Vacuolating Virus (SV-40). J. Nat. Cancer Inst. 29: 765-787 (1962)

4. Rabson, A. S., Kilham, L. and Kirschstein, R. L.; Intranuclear Inclusions in Rattus (Mastomys) Natalensis Infected with Rat Virus. J. Nat. Cancer Inst. 27: 1217-1223 (1961)

5. Friedman, R., Kirschstein, R. L., Borman, G. S. and Robbins, F.; Characteristics of Sabin Type I Poliovirus after Gastrointestinal passage in newborn infants: I. Monkey neurovirulence and temperature marker findings. Am. J. Hyg. 76: 137 (1962)

6. Rabson, A. S., O'Conor, G. T., Malmgren, R. and Kirschstein, R. L.; Simian Vacuolating Virus (SV-40) infection in cell cultures derived from adult human thyroid tissue. J. Nat. Cancer Inst. (Dec. 1962)

7. Rabson, A. S. and Kirschstein, R. L.; Introduction of malignancy in vitro in newborn hamster kidney tissue injected by simian vacuolating virus (SV-40); Proc. Soc. Exp. Biol. Med. 111: 233-238 (1962)

Serial No. DBS 33
1. Viral Immunology
2. Section on Pathology
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A

Project Title : Monkey Safety Test for Poliomyelitis Vaccine and Adenovirus Vaccine.

Principal Investigator: Dr. Ruth L. Kirschstein

Other Investigators : Dr. Gerald S. Borman, Mr. Ronald Clark, Mr. George Rusten

Cooperating Units : Serology Section screens monkey serums for freedom from antibody to poliovirus

Man Years:

Total	:	6.0
Professional	:	0.2
Other	:	5.8

Project Description:

Objectives: To test poliomyelitis and adenovirus vaccines for the presence of residual active virus particles that can only be detected by the direct inoculation of monkeys.

Methods Employed: As outlined by the PHS regulations for the above vaccines.

Major Findings: During 1962, 5 of 76 poliomyelitis vaccines and 0 of 11 adenovirus vaccines were tested for safety in monkeys. The central nervous systems of 50 monkeys were examined grossly and microscopically. No histologic lesions were found in any monkeys.

Significance to the Program of the Division: Integral part of the DBS program.

Proposed Course: This endeavor will continue in 1963 on the same scale.

Part B included yes/ X / no / /

Part B

Honors, Awards and Publications

1. Van Hoosier, G. L., Baron, S., Kirschstein, R. L. and Abinanti, F. R., The Safety Test for Poliomyelitis Vaccine; III. Comparative Sensitivity of Rhesus and Vervet Monkeys to Poliovirus. Am. J. Hyg., 75: 86-89 (1962)

Serial No. DBS 34
1. Viral Immunology
2. Section on Tissue Culture
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A

Project Title : The Tissue Culture Preparation and Tissue Culture Testing of Killed Virus Vaccines.

Principal Investigator: Dr. Paul Gerber and Dr. George A. Hottle

Other Investigators : Mr. Robert Grubbs

Cooperating Units : Monkey and rabbit tissues provided by the monkey safety testing unit.

Man Years:

Total	:	6.5
Professional	:	0.5
Other	:	6.0

Project Description:

Objectives: To prepare primary and continuous cell cultures for research and test purposes and to test vaccines for safety by tissue culture methods.

Methods Employed: The methods are those outlined in the PHS regulations and in the scientific literature.

Major Findings: During this year samples of 59 lots of Salk poliomyelitis vaccine (5 manufacturers), 12 lots of adenovirus vaccine (1 manufacturer), 3 experimental lots of adenovirus vaccine (1 manufacturer), 2 lots of adenovirus and Influenza vaccine, combined (1 manufacturer) and 2 lots of inactivated measles vaccine (1 manufacturer) were tested for safety in tissue culture. Simian virus SV-40 was found in 1 lot of poliomyelitis vaccine and in 1 lot of experimental adenovirus vaccine.

Significance of the Program to the Division:

Integral part of DBS testing program.

Proposed Course:

This is a continuing project.

Part B included yes / / no /X/

Serial No. DBS 34

Annual
Primary Culture Production

Annual Report for: November 1, 1961 - October 31, 1962

Type of Culture	Culture Productions: Tubes	2 oz.	Bottles MDB*	32 oz.
Monkey Kidney - Rhesus	136,413	61,564	1,251	554
Monkey Kidney - Vervet	68,559	4,965	2,395	260
Monkey Kidney - Black Mangabey	200	140	—	—
Rabbit Kidney	9,610	6,877	121	12
Hamster Kidney	40	49	—	—
Chick Embryo	6,370	22,142	100	32
Mouse Embryo	40	85	7	18
Guinea Pig Heart	171	8	—	—
Monkey Testes	200	8	—	—
Mouse Lung	92	—	—	—
Chicken Chorio Allantoic Membrane	—	13	—	—

*MDB Milk Dilution Bottles

No. and Type Tissues Processed		Volume Packed Cells	
Monkey Kidney - Rhesus	734	2,051.	cc
Monkey Kidney - Vervet	146	488.5	cc
Monkey Kidney - Black Mangabey	2	6.	cc
Rabbit Kidney	250	478.	cc
Hamster Kidney	21	4.5	cc
Chick Embryo	1,338	814.	cc
Mouse Embryo	91	20.5	cc
Guinea Pig Heart	16	2.5	cc
Monkey Testes	2	0.5	cc
Mouse Lung	60	2.0	cc
Chick Chorio Allantoic Membrane	10	0.4	cc

Serial No. DBS 35
1. Viral Immunology
2. Section on Viral Genetics
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A

Project Title : In vitro Tests on Live Poliovirus Vaccines

Principal Investigator: Dr. Paul Gerber

Other Investigators : None

Cooperating Units : None

Man Years:

Total	:	2.3
Professional	:	0.3
Other	:	2.0

Project Description:

Objectives: To determine the genetic characteristics and the concentration of poliovirus present in samples of oral, live poliovirus vaccine and to detect extraneous agents in such preparations.

Methods: The methods are those outlined in the PHS regulations and in the scientific literature.

Major Findings: One hundred twenty -eight samples of vaccines were tested. SV_{40} was detected in six samples and the release of such lots was withheld.

Significance of Program to the Division: Integral part of DBS testing program.

Proposed Course: This is a continuing project.

Part B included

yes /___/ no /_X_/

Serial No. DBS 36
1. Viral Immunology
2. Section on Viral Genetics
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A

Project Title : Virological Studies of Attenuated Polioviruses.

Principal Investigator: Dr. Paul Gerber

Other Investigators : Dr. Ruth L. Kirschstein

Cooperating Units : Section on Pathology, LVI, DBS

Man Years:

Total	: 1.8
Professional	: 0.3
Other	: 1.5

Project Description: Part I. Study of viral isolates from CNS of monkeys inoculated with attenuated Poliovirus.

Objectives: (a) To determine the fate of attenuated poliovirus inoculated into the CNS of monkeys.

(b) To study the effect of concentrated viral inocula in the monkey neurovirulence test.

Methods Employed: (a) Sections of brain and spinal cord taken at various levels are assayed for quantity of poliovirus and the genetic character of the viral isolates. The CNS material is also examined for presence of viral inhibitors, e.g., interferon.

(b) Concentration of live, oral poliovirus vaccines by ultracentrifugation or dialysis against Carbowax. Followed by virological studies of the CNS of monkeys inoculated with concentrated virus preparations.

Major Findings: These studies are still in progress. Preliminary results indicate that in certain instances a rct− type III polio vaccine during passage through the monkey CNS changes to rct+. Furthermore, there is an indication that virus recovery from the CNS is low or absent in paralyzed monkeys. The significance of this finding is as yet unknown.

Significance of Program to the Division: This study contributes to our knowledge of the properties of attenuated poliovirus.

Proposed Course: This is a continuing project.

Project Description: Part II. Determination of the possible immunochemical basis for neurovirulence of polioviruses.

Objectives: Attempt to demonstrate possible immunochemical difference between virulent and avirulent polioviruses.

Methods Employed: The first phase of this study consists of establishing a reproducable, sensitive test method which allows the detection of small amounts of poliovirus antigens. A quantitative complement fixation test is used for this purpose. Both crude and partially purified virus preparations are under study. If consistently significant differences are found between virulent and avirulent virus of the same serologic type, an attempt will be made to identify the chemical nature by means of hapten inhibition.

Major Findings: This study has just begun. No results are as yet available.

Significance of Project to this Division: To obtain basic information regarding the biological properties of polioviruses.

Proposed Course: Study will continue.

Part B included yes [ ] no [X]

Serial No. DBS 37
1. Viral Immunology
2. Section on Viral Genetics
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A

Project Title : Studies on Simian Virus-40.

Principal Investigator: Dr. Paul Gerber

Other Investigators : Dr. Ruth L. Kirschstein and Mr. Robert Grubbs

Cooperating Units : Section on Pathology, LVI, DBS
Section on Tissue Culture, LVI, DBS

Man Years:

Total	:	0.6
Professional	:	0.3
Other	:	0.3

Project Description: Part I. Relationships of SV-40 to Ependymomas Produced in Newborn Hamsters.

Objectives: To investigate certain aspects of virus-tumor relationships.

Methods Employed: Newborn hamsters were inoculated intracerebrally with increasing concentrations of SV-40. The brain and other tissues were examined for the presence of virus at various intervals after inoculation. Both tumor extracts as well as intact tumor cells were used for detection of virus.

Major Findings: At least $10^{6.5}$ $TCID_{50}$ of SV-40 was required to produce ependymomas. No viral multiplication in brain or other tissues was observed. The frequency of tumor formation and the length of the latent period were a function of the virus dose employed. No virus was detectable in extracts of brain tumors, while assay of intact tumor cells gave positive results.

Significance of Program to the Division: This study contributes basic information regarding the oncogenic properties of SV-40.

Proposed Course: This project is continuing to study the nature of the virus-tumor cell relationships.

Part B included yes /X/ no / /

Part B Awards, Honors and Publications.

1. Gerber, P. and Kirschstein, R. L.; SV-40 Induced Ependymomas in Newborn Hamsters; I. Virus-Tumor Relationships. (Virology, Dec., 1962)

2. Kirschstein, R. L. and Gerber, P.; Ependymomas produced after intracerebral inoculation of SV-40 into newborn hamsters. Nature, London. 195: 299-300 (1962)

Project Description: Part II. Detection of SV-40 in early lots of Salk Poliomyelitis Vaccines.

Objectives: To determine possible oncogenic effects in children vaccinated with Salk type poliomyelitis vaccine containing residual live SV-40. (The epidemiologic survey to be conducted by Dr. Michael Shimkin, NCI)

Methods Employed: Samples of poliomyelitis vaccine, inactivated, were tested for the presence of SV-40 by methods previously described (Proc. Soc. Exp. Med. Biol. 108: 205-209 (1961).

Major Findings: Of 32 samples of vaccines produced during the period of 1955 - 1957, 16 were found to contain detectable amounts of SV-40.

Significance of Program to the Division: Findings demonstrate the stability of SV-40 during storage at 4°C. The data obtained are potentially useful for future correlation with epidemiological surveys.

Proposed Course: This sub-project is completed.

Part B included yes / / no /X/

Serial No. DBS 38
1. Viral Immunology
2. Section on Animal Test
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A

Project Title : Investigations of the Serologic and Biologic Properties of the Simian Viruses.

Principal Investigator: G. L. Van Hoosier, Jr., D.V.M.

Other Investigators : None

Cooperating Units : Section on Tissue Culture, LVI

Man Years:

Total	:	2.0
Professional	:	0.3
Other	:	1.7

Project Description:

Objectives: To prepare reagents and acquire information needed to identify viral agents encountered in safety tests of poliomyelitis and adenovirus vaccine.

Methods Employed: Various serological, immunological and pathological techniques in general use in virology are employed.

Major Findings:

1. Antisera for the following simian viruses have been prepared in rabbits; SV-11, 12, 15, 16, 17, 18, 19, 20, 28, 41 and SA-12.

2. Hemagglutination inhibition appeared to be a suitable diagnostic technique for SV-2, 5, 12 and 36.

3. Simian viruses SV-1, 2, 4, 5, 12, 17, 28, 36 and 59 and SA-3, 4, 7 and 12 were found to be inactivated by desoxycholate, while SV-5 and herpes virus were resistant.

Significance to the Program of the Division: These studies provide data needed for the identification of viral agents encountered in vaccine safety tests and serve as a basis for the design of further investigation of simian viruses.

Proposed Course: This is a continuing project.

Part B included

yes /___/ no /_X_/

Serial No. DBS 39
1. Viral Immunology
2. Section on Animal Test
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A

Project Title : Studies on the Sensitivity of Cell Cultures to Poliovirus and SV-40.

Principal Investigator: G. L. Van Hoosier, Jr., D.V.M.

Other Investigators : None

Cooperating Units : Section on Tissue Culture, LVI

Man Years:

Total	:	0.4
Professional	:	0.1
Other	:	0.3

Project Description:

Objectives: To determine the sensitivity of cell cultures used for poliomyelitis vaccine safety tests to poliovirus and SV-40.

Methods Employed: Poliovirus is titrated in each tissue cell lot, both before and after use in the safety test. When tissue cell preparations are used for safety tests of poliovirus vaccine or for the detection of residual SV-40, sensitivity tests are carried out on the respective tissue cell lots. Only cell culture systems which show suitable sensitivity are considered acceptable for safety tests of vaccines.

Major Findings: All cell cultures examined have been consistently sensitive to poliovirus and SV-40.

Significance to the Program of the Division:

Provides control of sensitivity of safety test systems.

Proposed Course:

This continuing activity has been transferred to the Section on Tissue Culture.

Part B included yes / / no /X/

Serial No. DBS 40
1. Viral Immunology
2. Section on Serology
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A

Project Title : The Determination of Antipoliovirus Antibodies by the Metabolic Inhibition Test (MIT)

Principal Investigator: Dr. B. William Uhlendorf

Other Investigators : Miss Phyllis Fabisch and Mrs. Eva Brown

Cooperating Units : The Section on Tissue Culture, LVI

Man Years:

Total : 2.8
Professional: 0.4
Other : 2.4

Project Description:

Objectives:

1. To screen for the presence of antipoliovirus antibodies in pre-inoculation sera of animals used for testing poliomyelitis vaccine and poliovirus vaccine, live, oral, and in sera of other experimental animals.

To determine the level of antibodies in post-vaccination sera from monkeys and chicks used for poliomyelitis vaccine potency tests in sera of other experimental animals and in human sera.

2. To improve reliability of the MIT by modification of technique.

Major Findings:

1. During the year approximately 1800 sera of various species were titrated for content of antibodies against the three types of poliovirus and 5700 sera, (5300 monkey and 400 chick) were screened.

2. An improved plastic "cup-tray" has been designed and is now being used.

Significance to the Program of the Division: Integral part of DBS testing program.

Proposed Course: This is a continuing activity.

Part B included

yes /___/ no /X/

Serial No. DBS 41
1. Viral Immunology
2. Section on Serology
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A

Project Title : Standardization of Immune Serum Globulin (Human) for antibodies to the three types of poliovirus by the metabolic inhibition test. (MIT)

Principal Investigator: Dr. B. William Uhlendorf

Other Investigators : Miss Phyllis Fabisch

Cooperating Units : None

Man Years:

Total	:	0.5
Professional	:	0.2
Other	:	0.3

Project Description:

Objectives:

1. To determine whether the MIT is a satisfactory means of determining antipoliovirus antibodies in immune globulin preparations.

2. To obtain sufficient data to enable standards to be established for this product.

Major Findings: The MIT is a satisfactory means of assaying for antipoliovirus antibodies in immune globulin preparations. Based on data obtained for 81 lots of poliomyelitis immune globulin (representing 9 manufacturers) new standards of potency have been written. During the year 135 lots of globulin have been assayed by this test.

Significance of this Project to the Division: The work provides DBS with a basis for controlling the poliovirus antibody content of immune globulin preparations.

Proposed Course:

This is a continuing project.

Part B included

yes [ ] no [X]

Serial No. DBS 42
1. Viral Immunology
2. Section on Serology
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A

Project Title : The Antigenic Potency of Poliomyelitis Vaccine

Principal Investigator: Dr. B. William Uhlendorf

Other Investigators : Miss Phyllis Fabisch, Mrs. Eva Brown

Cooperating Units : Section on Pathology, LVI

Man Years:

Total : 1.5
Professional: 0.2
Other : 1.3

Project Description:

Objectives:

1. To determine the antigenic potency of poliomyelitis vaccine.

2. To develop an improved potency test.

Major Findings:

1. During the year 1 vaccine was tested by the monkey potency test and 28 were by a chick potency test of the graded response type involving the use of 12 monkeys and 1890 chicks.

2. The "factorial" potency test in chicks provides an estimate of the potency of an "unknown" vaccine in terms of its antigenicity relative to that of a "reference" vaccine. The standard error of the estimate can be calculated.

Significance to the Program of the Division: This is a portion of the DBS poliomyelitis vaccine control program.

Proposed Course: This is a continuing project.

Part B included

yes /___/ no /_X_/

Serial No. DBS 43

1. Laboratory of Viral Immunology
2. Section on Serology
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A

Project Title : Study of Inherited Metabolic Disorders in Human Diploid Cell Strains (HDCS)

Principal Investigator: B. William Uhlendorf, Ph.D.

Other Investigators : Albert I. Holtz, M.D.
Donald S. Fredrickson, M.D.

Cooperating Units : National Heart Institute, NIH

Man Years:

Total	:	0.7
Professional	:	0.5
Other	:	0.2

Project Description:

Objectives: To determine whether the biochemical manifestations of inborn errors of metabolism persist in cell cultures derived from tissues of individual with certain inherited diseases.

Methods Employed: 1) The initiation, serial propagation and preservation of euploid cell cultures;
2) Chromosome studies;
3) Thin layer chromatography;
4) Quantitative chemical analysis for phospho lipids, DNA, etc.;
5) Uptake of radio-isotope-labeled compounds.

Major Findings: Cell cultures have been established from tissues of two patients with lipidoses (Niemann-Pick Disease and Gaucher's Disease) and from five normal persons. Biochemical studies are in progress.

Significance of Program to the Division: The WHO has recommended that the potential of HDCS for production of viral vaccines be explored. The Project described here is highly significant in that the possibility exists that HDCS may carry and be capable of transmitting (via cell extracts), metabolic diseases.

Proposed Course: To continue the studies and publish the results in the scientific literature.

Part B included yes / / no /X/

Serial No. DBS 44
1. Viral Immunology
2. Section on Animal Testing
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A

Project Title : Studies on the mechanisms of recovery from viral infections and the role of interferon.

Principal Investigator: Dr. R. Steinmuller

Other Investigators : Dr. Samual Baron, NIAID
Dr. R. Friedman, NCI
Mr. C. Buckler, NIAID

Cooperating Units : Laboratory of Biology of Viruses, NIAID

Man Years:

Total	:	2.0
Professional	:	1.5
Other	:	0.5

Project Description:

Objectives: To elucidate the roles of the various factors responsible for resistance to and recovery from viral infections.

Methods Employed: Animal infection and/or immunization; suppression of the immune response by radiation, chemotherapy or neonatal thymectomy; culture and assay of virus, antibody and interferon in various in vivo and in vitro systems.

Major Findings: In recently published work we have shown that Guinea pigs rendered incapable of an antibody response or of delayed hypersensitivity by means of X-irradiation and chemotherapy recover normally from primary infection with vaccinia virus. Furthermore, such animals have significant titers of an interferon present at the sites of infection.

Significance of Program to the Division: This study is an attempt to delineate the relative roles of immunologic and non-immunologic mechanisms in the pathogenesis of virus diseases.

Proposed Course: This project has been terminated.

Part B included yes /X/ no / /

Part B

Honors, Awards and Publications:

Friedman, R., Baron, S., Buckler, C. and Steinmuller, R.; The Role of Antibody, Delayed Hypersensitivity and Interferon Production in the Recovery of Guinea Pigs from Primary Infection with Vaccinia Virus. J. Exp. Med. 116: 347-356 (Sept. 1962)

Serial No. DBS 45
1. Viral Immunology
2. Section on Animal Testing
3. Bethesda, Md.

PHS-NIH.
Individual Project Report
Calendar Year 1962

Part A

Project Title : Influence of Thymectomy on Pathogenesis of Virus Disease.

Principal Investigator: Dr. Robert Steinmuller

Other Investigators : None.

Cooperating Units : None.

Man Years:

Total	:	0.6
Professional	:	0.3
Other	:	0.3

Project Description:

Objectives: To elucidate the role of the thymus gland in the pathogenesis of viral infections.

Methods Employed: Surgical removal of thymus gland in neonatal mice; experimental infection and/or immunization; homografting of skin, thymus and other tissues; cell culture of thymus and other tissues; culture and assay of virus, antibody and interferon in various in vivo and in vitro systems.

Major Findings: Several laboratories in the past year have demonstrated that neonatal thymectomy in a variety of experimental animals leads to a loss of immunological capabilities to develop circulating antibodies, delayed hypersensitivity, homograft rejection, runt disease, autoimmune disease, etc. Work has been started to utilize this phenomenon as a further model for the study of viral infections in the absence of the immune mechanism.

Significance of Program to the Division: This study is an attempt to delineate the relative roles of immunologic and non-immunologic mechanisms in the pathogenesis of virus diseases.

Proposed Course: This is a continuing study.

Part B included yes / / no /X/

Serial No. DBS 46
1. Laboratory of Virology & Rickettsiology
2. Section on Basic Virology & Rickettsiology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A

Project Title: Antigenic Studies of Epidemic Typhus Rickettsiae

Principal Investigator: Dr. Lewellys F. Barker

Other Investigators: Miss Judith Kahn

Cooperating Units: None

Man Years: (calendar year 1962)
Total: 1
Professional: 1/2
Other: 1/2

Project Description:

Objectives: The objective is the investigation of the antigenicity and immunogenicity of three major fractions from purified preparations of epidemic typhus rickettsiae, strain E or Breinl. These fractions, i.e., a) extracellular, soluble material, b) cell walls and c) intracellular material, will be characterized according to their purity by physical and immunologic means and according to their ability to elicit protection in guinea pigs against infection and to produce toxin-neutralizing, complement fixing, Weil-Felix, fluorescent and precipitating antibodies in experimental animals (guinea pigs, mice and rabbits). Further fractionation will be attempted depending upon the results of the initial work.

Methods employed: Purification of rickettsiae in infected yolk sacs will be done by differential centrifugation, treatment with celite and albumin, and sucrose gradient centrifugation. Soluble antigen will be prepared by ether treatment of the rickettsiae. Cell walls will be separated from the intracellular material by disintegration of the purified rickettsiae in a Mickle apparatus. Standard techniques will be employed for determining protection in animals and in antibody responses.

Major findings: This project has just started. The equipment is being collected and the investigators are becoming facile with the techniques.

Significance to bio-medical research and program of the division.
It has been almost two decades since this problem was last studied systematically. At that time, during the war years, the primary emphasis was on the development of a satisfactory typhus vaccine. The advances in concepts and techniques since the earlier studies warrant reexamination of the subject.

Part B included Yes___ No X

Serial No. DBS 47

1. Laboratory of Virology & Rickettsiology
2. Section on Basic Virology & Rickettsiology
3. Bethesda 14, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A

Project Title: General Aspects of Virology and Rickettsiology

Principal Investigator: Dr. Joseph E. Smadel

Other Investigators: Miss Elizabeth B. Jackson

Cooperating Units: None

Man Years: Inconsequential

Project Description:

Objectives: This particular project is included among those of the Laboratory of Virology and Rickettsiology in order to provide a mechanism for reporting work which does not fall clearly within the purview of other project reports. One of the most important duties of this laboratory is to keep abreast of advances in the expanding field of virology, especially as they relate to the development of new vaccines. One way of doing this is by attendance at and participation in various conferences and symposia. The report lists several publications in the general field of immunology, virology and rickettsiology.

Major findings: Principal investigator organized and chaired a Symposium on "Immunization Against Arbor Virus Infections" held during the annual meeting of The American Society for Tropical Medicine and Hygiene in Atlanta in early November 1962.

The salient points of the Symposium as they bear on the mission of the DBS were as follow:

(1) An inactivated Rift Valley fever vaccine prepared from monkey kidney tissue cultures by techniques analogous to those used in manufacturing Salk vaccine is potent and safe in animals and in man. Vaccines made by pilot plant procedures have been employed in over a thousand persons. Information at hand is adequate to proceed towards licensing of commercially produced vaccine with a minimum of delay, should such a step be warranted.

(2) Progress is being made by several groups of investigators toward the development of attenuated viral strains that might be used in vaccines against dengue fever and against encephalitis caused by Japanese, Western or Venezuelean viruses. None of these four attenuated vaccines is sufficiently well developed at present so as to be a likely candidate for licensing and commercial production within the next year or so.

(3) The large number of arborviruses and the frequent occurrence of several which produce disease in man in the same geographic area, has presented a problem in immunoprophylaxis equal in complexity to that associated with immunization against respiratory viral infections. A small ray of light is beginning to show in the arborvirus field. Infection caused by certain viruses induce slight but definite immunity against certain other viruses in the same Casals' group. By serial infection with attenuated strains of selected viruses in Casals' B group it has been possible, in experimental animals, to induce a broad immunity which encompasses members of the B group not included in the immunization program. This basic approach hopefully will help solve the problem of immunoprophylaxis against arborviruses, however, even with an optimistic viewpoint, the solution cannot be expected for years.

Part B included: Yes

PHS-NIH
Individual Project Report
Calendar Year 1962

Part B Honors, Awards, and Publications

Publications other than abstracts from this project:

Smadel, J. E.: Rocky Mountain spotted fever vaccine. In Symposium on Spotted Fever Group of Rickettsiae. Med. Sci. Pub. No. 7, Walter Reed Army Institute of Research, U.S. Govt. Printing Office 1960, pp 55-61. (This article listed as in press in 1960 was published in December 1961.)

Woodward, T. E. and Smadel, J. E.: The rickettsioses. In Harrison, T.R. (ed.): Principles of Internal Medicine (ed. 4) New York, McGraw-Hill Book Co., Inc., 1962 pp 1090-1108. (Listed in 1961 as in press.)

Smadel, J. E.: Epidemic Hemorrhagic Fever. Ibid. pp 1186-1188. (Listed in 1961 as in press.)

Smadel, J. E.: Report on Session III. International Conference on Measles Immunization. Am. J. Dis. Child. 103: 393-394, 1962.

Smadel, J. E.: Future of measles vaccines. Scientific problems remaining unanswered. Am. J. Dis. Child. 103: 520-521, 1962. (Listed in 1961 as in press.)

Smadel, J. E.: Rocky Mountain spotted fever. In McDermott, W., and Beeson, P. B. (eds.): Cecil-Loeb Textbook of Medicine (ed. 11) Philadelphia, W. B. Saunders Co., in press.

_____: Tick-borne rickettsioses of the Eastern Hemisphere. Ibid.

_____: Rickettsialpox. Ibid.

_____: Scrub typhus. Ibid.

_____: Smallpox. Ibid.

_____: Vaccinia. Ibid.

Honors and Awards relating to this project:

Joseph E. Smadel, M.D. - 1962 Honorary D.Sc. degree conferred by the University of Maryland.

1962 Albert Lasker Award for Clinical Research presented by the Albert and Mary Lasker Foundation.

Serial No. DBS 48
1. Laboratory of Virology & Rickettsiology
2. Section on Basic Virology & Rickettsiology
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1962

Project Title: Growth and Metabolism of Rickettsiae

Principal Investigator: Mrs. Hope E. Hopps

This project was continued during calendar year 1962 and is being reported under project title: Mechanisms of Intracellular Infection.

Serial No. DBS 49
1. Laboratory of Virology & Rickettsiology
2. Section on Basic Virology & Rickettsiology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A

Project Title: Mechanisms of Intracellular Infection

Principal Investigator: Mrs. Hope E. Hopps

Other Investigators: Miss Elizabeth B. Jackson
Mrs. Barbara C. Bernheim
Dr. Joseph E. Smadel
Dr. Seiya Kohno (Guest Worker)

Cooperating Units: None

Man Years:
Total: 1
Professional: 1
Other: 0

Project Description:

Objectives: The main objective of this long, continuing project is the accumulation of information concerning the mammalian host cell and its response to microbial infection with particular emphasis on the carrier state and the means by which infected cells are freed of their parasites.

Methods employed: Modern tissue culture techniques and the standard procedures used in a research laboratory engaged in studies on viral and rickettsial agents were employed.

Major findings: The hypothesis under investigation at the present time concerns the possible presence in cells infected with rickettsiae of a substance analogous to viral interferon which may assist in clearing the cells of their infection. The outlined approach is to compare the action of viral interferon and preparations processed similarly designated "rickettsial interferon" on both a test virus system and on cells infected with rickettsiae. At the present state of the work no meaningful data are available.

Significance of the program to the Institute: The behavior of infected cells, particularly with regard to latency and the carrier state, is

among the more important problems facing those interested in the control of infectious diseases.

Proposed course of the project. The present study concerning interferon-like substances in rickettsiae will be completed in the coming year and it is hoped that studies concerning the fate of rickettsiae in immune and nonimmune cells in vitro can be undertaken. While this general project is not worked on continuously, experiments are initiated as new concepts and techniques present themselves.

Part B included Yes X No

PHS-NIH
Individual Project Report
Calendar Year 1962

Part B

Honors, Awards and Publications

Publications other than abstracts from this project:

Smadel, J. E.: Intracellular Infections. Presented at the Lasker Medical Research Award Winner's Program, New York Academy of Medicine, November 14, 1962. Bull. N. Y. Acad. Med. (in press).

Serial No. DBS 50
1. Laboratory of Virology & Rickettsiology
2. Section on Basic Virology & Rickettsiology
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A

Project Title: Studies on a Possible Psittacosis-like Agent Isolated from Cercopithecus aethiops Tissue Culture Material

Principal Investigator: Mrs. Hope E. Hopps

Other Investigators: Miss Elizabeth B. Jackson
Mrs. Barbara C. Bernheim

Cooperating Units: None

Man Years: (calendar year 1962)
Total: 1
Professional: 1
Other: 0

Project Description:

Objectives: The primary objective of the project is the biological characterization of the agent and the determination of its prevalence in terms of specific antibody in sera from normal monkeys.

Methods Employed: Modern tissue culture and embryonated egg techniques and the standard serologic procedures used in studies in viral and rickettsial agents were employed.

Major Findings. In the course of experiments concerning the ability of SV_{40} to proliferate in embryonated eggs, material from the 7th consecutive passage was titrated in BS-C-1 cells. The inoculated cultures failed to show the characteristic changes associated with SV_{40} multiplication, but their granular appearance suggested the possible presence of another agent. Subsequent experiments revealed that the agent came directly from the SV_{40}-containing monkey tissue culture material used to inoculate the embryos. The agent is visible by ordinary light microscopy, grown only intracellularly, is sensitive to chloromphenicol but refractory to penicillin and streptomycin, and does not appear to be a fastidious bacterium or PPLO agent. Preliminary serologic tests suggest that the agent may be a member of the psittacosis-lymphogranuloma group.

Significance of the Program to the Institute. The characterization of new agents isolated from primate tissue cultures is of importance since these tissues serve as a source for virus vaccines.

Proposed Course of the Project. Studies concerning the identification of the agent are being continued and some estimate of its prevalence will be made by examining sera from "normal" monkeys for presence of specific antibody.

Part B included Yes No X

Serial No. DBS 51
1. Laboratory of Virology & Rickettsiology
2. Section on Basic Virology & Rickettsiology

PHS-NIH
Individual Project Report
Calendar Year 1962

Project Title: Studies with Simian Virus 40. Development of a Continuous Tissue Culture Cell Line from Cercopithecus aethiops kidney Tissue

Principal Investigator: Mrs. Hope E. Hopps

This project was continued during calendar year 1962 and is being reported under project title: Development of Continuous Tissue Culture Lines for Use in Testing of Vaccines.

Serial No. DBS 52

1. Laboratory of Virology & Rickettsiology
2. Section on Basic Virology & Rickettsiology
3. Bethesda 14, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A

Project Title: Development of Continuous Tissue Culture Lines for Use in Testing of Vaccines

Principal Investigator: Mrs. Hope E. Hopps

Other Investigators: Mrs. Barbara C. Bernheim
Mr. Albert L. Giles
Dr. Ananda Nisalak (Guest Worker)
Dr. J. H. Tjio (NIAMD)

Cooperating Units: Laboratory of Experimental Pathology, NIAMD

Man Years: (calendar year)
Total: 2
Professional: 1½
Other: ½

Project Description:

Objectives: A. One objective of this project, i.e., the establishment of a simian virus 40 susceptible Cercopithecus kidney cell line has been accomplished; the line has been designated BS-C-1. Extensive interest in the line for other purposes including the titration of measles virus, and the demands of other laboratories for these cells have led to more detailed studies of its biological characteristics. B. The second objective of the project is to establish a line of chick embryo cells suitable for use in testing for the presence of RIF, a virus of the fowl leucosis complex, in live measles vaccine.

Methods employed: Modern tissue culture techniques and the ordinary procedures used in tissue culture techniques and the ordinary procedures used in tissue culture research were employed.

Major Findings: A. BS-C-1 Tissue Culture Cell Line. The BS-C-1 culture initiated in March 1960, is now in its 125th passage and is considered to be an established cell line. Cultures have been sent to the Cell Bank Committee (sponsored by NCI) for characterization and subsequent storage at the American Type Culture Collection. The BS-C-1 line is unique in the fact that this is the only reported continuous culture whose chromosomal pattern and virus susceptibility have been studied in concert since early passage levels. Findings indicate that while the chromosomal pattern of the cells changed from diploid (30th passage) to subdiploid (at 41st passage) to heteroploid (111th passage), the cells have not changed their sensitivity to SV40 virus. Moreover, at the 108th passage they were still sensitive to attenuated measles virus. Further evidence of their stability with regard to virus proliferation was noted in studies with influenza A and B and adenoviruses 3,4 and 7. The BS-C-1 line was refractory to these agents at low passage and still failed to support their growth at the 95th passage level. In addition to those viruses already reported to multiply in BS-C-1 cells, i.e., SV40, measles, and attenuated polioviruses 1,2 and 3, it has been shown that this line will also support multiplication of Rift Valley fever virus, RS virus, O'Malley's A-1 agent, simian viruses 1,4 and 5, Coxsackie A9, and a psittacosis-like agent isolated in this laboratory but as yet not identified. Moreover, preliminary data suggest that the line may be useful in basic studies with epidemic typhus rickettsiae. B. Chick Embryo Tissue Culture Cell Line. Only selected embryos known or presumed to be RIF-free were employed in the experiments. Trypsinized whole embryo preparations were maintained in several types of tissue culture media. Seventeen separate attempts have been made to cultivate cells prepared in this fashion. At the present time only one of the lines, BS-CE-17, has shown evidence of survival beyond the 18th passage. This line is now in its 31st passage but its growth rate has decreased and survival of the line is questionable.

Significance of the Program to the Institute. A. BS-C-1 Cell Line. The primary importance of the BS-C-1 line is its usefulness in testing for the presence of SV40; it provides a reliable sensitive noncontaminated source of Cercopithecus cells for diagnostic isolation of SV40. Moreover, its sensitivity to measles virus, coupled with the fact that the cells can be easily grown and maintained, suggest that it might be useful in the measles diagnostic research laboratory.

B. Chick Embryo Cell Line. Among the numerous technical difficulties inherent in the present RIF assay procedure is the necessity for a continuous weekly supply of known RIF-free chick embryos. The establishment of a RIF-sensitive chick embryo tissue culture line would solve one of the major problems in measles vaccine testing.

Proposed Course of the Project. A. BS-C-1 Cell Line. It is anticipated that experimental work with the line during the next year will be minimal. However, the line will continue to be maintained in this laboratory, will be monitored for susceptibility to SV40 and measles, and will be distributed to other interested laboratories as requests are received; thus far in 1962, 46 laboratories have requested cultures. B. Chick Embryo Cell Line. Studies will continue with the chick embryo cultures now being carried in the laboratory; however, the uniformly discouraging results obtained to date suggest that this approach may be abandoned in the near future. The possibility of using frozen stocks of early passage chick embryo cells, analogous to the system used at the Wistar Institute for human fetal cells, is being considered.

Part B included Yes X No

PHS-NIH
Individual Project Report
Calendar Year 1962

Part B

Honors, Awards and Publications

Publications other than abstracts from this project:

Meyer, H. M., Hopps, H. E., Rogers, N. G., Brooks, B. E., Bernheim, B. C., Jones, W. P., Nisalak, A. and Douglas, R. D., Studies on simian virus 40, J. Immunol., 88: 796, 1962. (Reported in 1961 as in press).

Serial No. DBS 53

1. Laboratory of Virology & Rickettsiology
2. Section on Basic Virology & Rickettsiology
3. Bethesda 14, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A

Project Title: Typhus Vaccine - Living Attenuated Strain E

Principal Investigator: Miss Elizabeth B. Jackson

The project reported under this title for the years 1960 and 1961 is reported in 1962 under the title of Rickettsial Vaccines.

Serial No. DBS 54

1. Laboratory of Virology & Rickettsiology
2. Sections on (1) Basic Virology & Rickettsiology, (2) Respiratory Viruses
3. Bethesda 14, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A

Project Title: Rickettsial Vaccines

Principal Investigator: Miss Elizabeth B. Jackson

Other Investigators: Dr. Joseph E. Smadel, Dr. J. Anthony Morris and Mr. Calvin G. Aulisio (LVR, DBS)

Capt. James R. Kingston and Cdr. H. H. Bloom (Navy)
Col. Abram S. Benenson and Dr. Sanford L. Berman, (WRAIR)

Cooperating Units: Bureau of Medicine and Surgery, Department of the Navy; Naval Medical Field Research Laboratory, Camp Lejeune, North Carolina.
Department of Biologics Research, Division of Communicable Disease and Immunology, Walter Reed Army Institute of Research.

Man Years:
Total: 1½
Professional: 1
Other: ½

Project Description:

Objectives: A. Improvement of established rickettsial vaccines. B. Development of new rickettsial vaccines.

Methods employed: Standard procedures used in a research laboratory engaged in studies on rickettsial agents.

Major findings: A. Typhus vaccine - killed epidemic. This study was undertaken (1) to determine the minimum dose of licensed commercial epidemic typhus vaccine which would elicit demonstrable antibody in the majority of recipients, and (2) to determine the size of the primary dose necessary to prepare the individual recruit so that he would respond in a booster fashion when given additional vaccine at a later date.

As reported last year, groups of 75-100 Marines were given a primary course of immunization with decreasing amounts of commercial epidemic typhus vaccine. Analysis of the results of serological tests indicated that injection of as little as 1.0 ml of a 1:4 dilution of vaccine elicited detectable complement fixing (CF) and toxin neutralizing (TN) antibodies in 91 percent of recruits. Furthermore, the injection of 1.0 ml of a 1:64 or a 1:256 dilution of the vaccine induced detectable antibodies in a small proportion of men.

Six months after the primary course, men from each group received a booster dose of 0.5 ml of undiluted vaccine; in addition, a control group of previously unvaccinated men were similarly inoculated. Although all the men in this control group developed antibodies, the mean TN antibody response to the booster dose in five of the previously vaccinated groups was significantly higher, on statistical analysis, than in the control group. Furthermore, even members of the group that received primary immunization with the highest dilution of vaccine, i.e., the 1:256 dilution, had been "prepared" although they did not acquire detectable antibodies. Members of this group responded to the booster dose by developing levels of antibody which were somewhat higher than those obtained in the control group although the difference was not statistically significant.

Because of the unexpectedly good response obtained with this one lot of vaccine, a review of potency test data on all lots of epidemic typhus vaccine released from January 1958 to March 1962 was undertaken. This indicated that all the vaccines were of comparable potency. Hence, equally good results could be expected in man with any of them.

On the basis of results obtained in this study, the military services will change their primary course of immunization with typhus vaccine from 2 doses of 1.0 ml to a single dose of 0.5 ml. This change is now being implemented.

Proposed course of project: The results were considered sufficiently promising by the participating groups to warrant continuation of the study dealing with minimal amounts of typhus vaccine required to "prepare" the recruit so that he might respond in a booster fashion when given typhus antigen at a future time. A study similar to the previous one will be carried out in groups of Marines who will receive varying amounts of a selected lot of commercial typhus vaccine (1.0 ml doses of 1:16 to 1:1028 dilutions of vaccine) followed by a booster dose of 0.5 ml of 1:16 dilution given three months later; control groups will be included. Responses will be followed by laboratory studies on sera obtained at appropriate times. The laboratory work for this study will be performed principally by Dr. Lewellys Barker and Judith Kahn who joined the Section of Basic Virology and Rickettsiology, LVR, in July 1962.

B. Typhus vaccine - living attenuated Strain E. This study was undertaken (1) to develop procedures for the production and lyophilization of stable high titer living attenuated epidemic typhus vaccine, Strain E, and (2) to develop an acceptable reliable infectivity assay to serve in biologics control. Studies were also carried out in guinea pigs on the correlation of antibody response with resistance to infection. The main objectives have been achieved and reported in detail in reports of the preceding two years.

A pilot lot of freeze dried vaccine has been prepared consisting of some 1200 vials each of which contains 1 ml of a 20% yolk sac suspension. This material, which is stored at -20°C at WRAIR, has an embryo lethal titer of $10^{-6.6}$. Aliquots of this material, stored at 35°C for 4 weeks, had an ELD_{50} of $10^{-4.0}$.

The basic seed for production of Strain E vaccine, which has been supplied by Dr. Charles L. Wisseman, Jr. of the University of Maryland Medical School, is to be tested for avian leukosis virus and other adventitious agents.

C. Q fever vaccine - killed. Formalin inactivated experimental Q fever vaccine, prepared in embryonated eggs, is an excellent immunizing agent which protects man against airborne infections with R. burneti. The principal problem associated with its use is encountered among individuals who have been sensitized by prior exposure to R. burneti and who react unfavorably when given the vaccine.

Field studies are in progress to determine whether a course of immunization starting with a small inoculum of 0.1 ml of undiluted vaccine and increasing to the usual dose of 1.0 ml can be used successfully without prior screening of vaccinees, by means of skin and serological tests, to eliminate those who might be sensitive. A pilot lot of vaccine prepared by the Department of Biologics Research, WRAIR, is being used for these studies which have been undertaken in various parts of the USA. A standard protocol has been provided all participants as well as standard data sheets for recording histories and reactions.

Satisfactory procedures for the determination of safety (inactivation of R. burneti) and potency (an antigenic extinction test in guinea pigs) of Q fever vaccine have been developed and reference Q fever vaccine and antiserum are on hand in the DBS.

Regulations for the commercial production of licensed inactivated Q fever vaccine are in semifinal draft form.

Significance to biomedical research and the program of the Division. Rickettsial diseases are of continuing concern to the military services and might well become of importance throughout the world following devastations such as might be brought about by nuclear attack. It is, therefore, important that steps be taken to produce and stockpile stable

and potent rickettsial vaccines. It is also important to review immunization procedures from time to time to ensure that an adequate but not excessive antigenic mass is being administered and to consider the feasibility of a polyvalent vaccine.

Proposed course of projects - Indicated in main discussion of each topic.

Part B included: no

Serial No. DBS 55

1. Laboratory of Virology & Rickettsiology
2. Section on General Virology
3. Bethesda 14, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A

Project Title: Investigations Concerned with Human Hepatitis Virus

Principal Investigator: Dr. Joseph P. O'Malley

Other Investigators: Mr. John F. Thiel (LBB, DBS)

Cooperating Units: None

Man Years:
Total: 2½
Professional: 1½
Other: 1

Project Description:

Objectives: The purpose of this project is (1) to develop suitable laboratory methods for cultivating and handling one or more of the human hepatitis viruses and (2) to evaluate the importance to man of certain viruses presumed to cause human hepatitis.

Methods employed: The tissue culture methods of a virus research laboratory are employed in this work. In studies on A-1 virus, particular use is made of a plaque counting technique with chick embryo monolayers serving as the host system in diagnostic isolation and neutralization tests.

Major findings: Previous reports have described a number of the general properties of the A-1 virus, an agent isolated from primary rabbit kidney tissue cultures inoculated with an aliquot of the NIH icterogenic plasma pool. Of particular interest were the serological findings with specimen taken from volunteers who, a decade ago, developed serum hepatitis with jaundice following inoculation with NIH icterogenic materials. Significant increases in antibody against the A-1 virus occurred in 93% of the 30 persons whose serial sera were tested.

During the past year attention has been directed to those volunteers who did not develop jaundice following inoculation with the same materials used for the group mentioned above. Of the 17 persons from whom serum

specimens were available before inoculation of infectious material, 14 possessed antibody against the A-1 virus in titers ranging from 1:10 to 1:40, with the majority having values of 1:20. The three persons in the group of 17 who had no A-1 virus antibodies at the time of inoculation developed significant levels a month or two later. Among the 14 volunteers whose serum was positive before the injection of icterogenic material, 11 subsequently showed a fourfold or greater increase in antibody levels, 2 increased twofold and 1 maintained a stationary level. Thus, serologic studies on volunteers who failed to develop jaundice after inoculation with proven icterogenic materials suggest that these persons had had previous experience with A-1 virus and that this might account for the failure of clinical disease to appear.

A study has been initiated to determine the frequency of occurrence of A-1 virus antibody in specimens of convalescent serum obtained from persons who had hepatitis while living in various parts of the United States, Canada, Brazil, Chile, Korea, and Italy. Four hundred of the 444 specimens tested came from cases considered to be infectious hepatitis. Of these 400 specimens, 18 or 4.5% contained A-1 virus antibody; 12 had a titer of 1:10, 2 of 1:20, 1 of 1:40, 2 of 1:80 and 1 of 1:320. A-1 virus antibody was found in 4 of 44 specimens from persons who were considered to have serum hepatitis; 2 of these had titers of 1:10 and 2 of 1:20. However, 26 of the 40 specimens which showed no A-1 virus antibody were taken 9 or more months after jaundice had cleared; only a few in the group of 400 were obtained so late. Data from the studies on volunteers reported earlier had shown that detectable A-1 virus antibody disappeared in 75% of 24 persons 9 or more months after jaundice had cleared. The failure to detect A-1 virus antibody in these 26 sera is consistent with previous findings. Of the remaining 14 specimens which did not contain A-1 virus antibody 12 were taken during jaundice at a time probably too early for antibody to have developed. Data were unavailable regarding the phase of the disease at which the remaining 2 specimens were drawn, but neither had signs of elevated bilirubin. Thus, A-1 virus antibody was found in 4 of 6 specimens in which it might have been expected to have occurred.

Many attempts have been made to isolate transmissible agents from additional icterogenic materials employing a number of different tissue culture systems. No significant data has yet come from this work.

Earlier in this project great difficulty was encountered in the preparation of a satisfactory animal antiserum against the A-1 virus. Since that time the guinea pig has been found to be a suitable animal for this purpose and A-1 virus antiserum having a neutralization titer of 1:80 has been prepared.

In an effort to determine the frequency with which A-1 virus is associated with cases of hepatitis that occur among persons who have received multiple blood transfusions, preoperative and postoperative serum specimens are

being collected from patients undergoing cardiac surgery at the Clinical Center. None of the 40 serum pairs tested to date have been positive for A-1 virus antibody. Although one of these 40 persons developed jaundice following operation, his disease appears to have no relation to A-1 virus infection since he did not develop A-1 virus antibody during convalescence.

Since the plaque reduction neutralization test consists of a complicated series of procedures, it is essential that the reliability of the test be demonstrated. In order to do this, 126 duplicate serum specimens, taken from the jaundiced volunteers mentioned above, were given two different codes and then tested for A-1 virus antibody. After the tests were completed and the specimens decoded, it was found that 92% of the 126 specimens varied twofold or less when the results were compared. From these data it was concluded that the A-1 plaque neutralization test method was reliable.

The tissue culture host range of the A-1 virus has been extended to include primary human embryonic kidney and the continuous cell lines of (1) rhesus monkey heart (Salk), (2) BS-C-1 Cercopithecus kidney (Hopps), and (3) human embryonic lung (Davis).

Significance to biomedical research: The threat of serum hepatitis contamination of whole blood and blood derivatives as well as the continued significance of infectious hepatitis in civilian and military populations makes the control of these diseases one of the major unresolved problems of contemporary virology.

Proposed course of the project: Studies with the A-1 virus will be continuing with emphasis placed on determining the importance of the role this virus plays in human hepatitis. Specimens from hepatitis outbreaks will continue to be tested for isolatable agents as well as for the presence of antibody against A-1 virus. Studies are also underway to determine the electron micrograph characteristics of this virus.

Serial No. DBS 56

1. Laboratory of Virology & Rickettsiology
2. Section on Virus Biology
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1962

Project Title: Studies on Antimicrobial Activity of Preparations from Abalones and Oysters and Other Materials

Principal Investigator: Dr. Chen Pien Li

This project was continued during calendar year 1962 and is being reported under project title: Studies on Antimicrobial Agents.

Serial No. DBS 57
1. Laboratory of Virology & Rickettsiology
2. Section on Virus Biology
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A

Project Title: Studies on Antimicrobial Agents

Principal Investigator: Dr. Chen Pien Li

Other Investigators: Dr. Benjamin Prescott* (NIAID)
Dr. C. W. Hiatt (LBB)
Dr. Carl F. T. Mattern**(NIAID)
Mrs. Lotta Chi***(NIAID)
Mr. Elmer C. Martino

Cooperating Units: *Laboratory of Bacterial Chemistry (NIAID)
**Laboratory of Virus Biology (NIAID)
***Laboratory of Virus Biology (NIAID)

Man Years:
Total: 4 1/4
Professional: 3/4
Others: 3 1/2

Project Description:

Subproject I. Antimicrobial Activity of an Oyster Fraction

Objectives: Our main object is to purify and test oyster fractions, the preparation of which was described in last year's annual report.

Methods Employed: For purification, the alcohol fractionation method was used. To a 10% water solution of the oyster fraction, a quantity of cold 95% alcohol equal to one-half the volume of the solution was added and the mixture was kept at 4°C overnight. The precipitation thus formed was taken in H_2O and lyophilized. This process was repeated 4 times, the volume of alcohol being increased each time.

For assay in mice a moderately virulent strain of Streptococcus pyogenes, beta-hemolytic strain was used for intraperitoneal inoculation, producing approximately 70% abscesses and 40% deaths in the infected animals in 50 days. The mice were fed with varying quantities of the oyster fraction for 2 weeks, starting 3 days before infection.

Major Findings: Assay experiments with the unpurified fraction were carried out, using 200 mice for treatment and control. When the daily feeding dose was 2 mg per mouse, the death rate of the infected mice was reduced from 44% in the control animals to 10% in the treated ones.

The purified material has not yet been tested in animals. In in vitro test, one of the purified preparations was active against Staphylococcus aureus even when diluted to more than one part per million.

Significance to Bio-medical Research: At present there are certain bacterial infections in human beings which do not respond to any known antibiotics. Since the active oyster material is nontoxic, so far as we know, its purified form may have therapeutic possibilities.

Proposed Course: Our present method of purification can yield only a very small quantity of active substance. Further investigation aimed at mass production is warranted.

Further work for purification of the antiviral fraction is also desired.

Subproject II. Antiviral Activity of Psoralen Compounds

Objective: For a number of years 8-methoxypsoralen has been used effectively for the treatment of leukoderma in man, and more recently it and related compounds have been employed extensively to accelerate suntanning. Our object is to test it and two of its related compounds, namely, 5-methoxypsoralen and 2', 4, and 8-trimethylpsoralen, for antiviral activity against poliovirus and influenza virus infections in tissue cultures or in mice.

Methods Employed: The same tissue culture methods and animal experimental methods described in our previous annual reports were used.

Major Findings: In tissue culture the 5-methoxy derivative strongly inhibited LH-v virus, a variant of type III poliovirus Leon strain. It also inhibited Sabin types I and II, but not type III virus used in the live poliovaccine. The 8-methoxy compound showed moderate inhibition against all virulent and attenuated types I, II and III virus. The 2, 4, 8-methyl derivative was tested only against types I and III attenuated virus, and it showed only feeble activity.

Swiss mice weighing 20 to 23 gms were fed daily with varying dosages of the drug 8-methoxypsoralen for 5-6 days before inoculation of virus and 6-9 days afterwards. Groups of 30 treated mice, along with the same number of controls, were inoculated intracerebrally with type I poliovirus and observed for 12-14 days. The results indicate that paralysis or death occurred less frequently in infected mice treated with the drug than in the untreated control animals. For example, in one experiment even as little as 0.005 mg per mouse per

day by mouth reduced the death rate from 48% in the controls to 23% in the treated animals.

Mice were infected intranasally with influenza B virus, and fed with the drug for a week beginning one day after infection. Larger doses of 8-methoxypsoralen, i.e., 0.5 to 1.0 mg/mouse/day, were employed under these conditions with influenza virus to induce a protective effect in mice than were employed in the mice inoculated with poliovirus. In one typical experiment the death rate for 30 treated mice was 47% and that for 30 control mice was 74%.

Significance to Bio-medical Research and the Program of the Division. The present experiments demonstrated for the first time that some of the furocoumarins possessed antiviral activity against polioviruses and influenza virus. There are numerous furocoumarins either existing in nature or synthesizable. Among those furocoumarins studied, the drug 8-methoxypsoralen has been used clinically for a number of years to treat human vertiligo and accelerate suntanning. It has been proven to be of low toxicity. Further study of its antiviral effect might reveal its practical chemotherapeutic, or chemoprophylactic, value for man or animal. Moreover, we also have been using these drugs for further attenuation of Sabin III poliovirus used in oral vaccine.

Subproject III. Isolation of Antiviral and Antibacterial Substances from Calf Thymus

Objectives: The thymus has been one of the baffling glands in the body and its function has not been clear. Recently, different investigators have established the fact that thymus is related to immune response. Metcalf has extracted a lymphocytosis-stimulating factor (LSF) from mouse or human thymus, and considered it as a hormone. This factor directly stimulated lymphopoietic cells and also suppresses the adrenal corticoids which causes lymphopenia. In the current year Szent-györgyi announced the discovery of 2 hormones isolated from calf thymus: "promine," (growth promoting) and "retine" (growth retarding). The latter inhibited malignant growth in the mouse , while the former promoted cell growth and also induced sterility in the same animal. Our objective is to investigate whether extract made from calf thymus possesses any antiviral and antibacterial activity.

Methods Employed: After the fat was removed, the fresh calf thymus gland was homogenized in a Waring blendor with 2 volumes of distilled water or 25% acetic acid. The mixture was placed at 4°C for 72 hours (adjusted to pH 5.0 when acetic acid was used for extraction) and centrifuged to remove the sediment. The supernate was dialized against distilled water at 4°C for 48 hours, filtered through an E.K pad and lyophilized. The average yield of 5 lots was around 0.5% of the wet weight of the thymus material. The product is a white powder, readily soluble in water.

The tissue culture methods used for assay are the same as those described in our previous annual reports.

Assay work in mice was carried out as follows: Different litters of newborn mice were treated intraperitoneally with a single dose of the extract for each mouse varying from 1 ug to 100 ug. These mice, along with untreated controls, were challenged at different time intervals before or after treatment with 5 to 15 $TCID_{50}$ of Coxsackie A-9 virus administered intramuscularly.

Major Findings: In tissue culture, the results showed that the presence of 4 to 100 ug/ml of the thymus extract reduced the yield of Coxsackie A-9 virus from $10^{6.1}$ ($TCID_{50}$) to $10^{4.1}$ or $10^{2.1}$ respectively. Comparable results were obtained in a series of more than 10 experiments.

The thymus extract did not directly inactivate the Coxsackie A-9 virus *in vitro* in absence of living cells.

Perhaps more interesting was the observation that the thymus extract protected mice from experimental infection with Coxsackie A-9 virus. The extract exerted no apparent toxicity in newborn Swiss albino mice. In more than 10 experiments carried out at different dates, more than 200 litters of mice were used for treatment and control. There seemed to be an optimal dose response. Generally speaking, when the optimal dose was used, the rates of death were 20 to 50% lower in the treated animals than in the controls and the incubation periods of death were, in general, several days longer in the treated mice. However, if the dose of the thymus extract was larger or smaller than the optimal, no protective effect was observed. One typical experiment may be mentioned here. Twelve litters of 82 newborn mice were treated with a single dose of 2.5 ug/mouse of thymus extract given intraperitoneally 5 hours after infection. These mice, along with 10 litters of 73 control mice, were infected intramuscularly with 15 $TCID_{50}$ of Coxsackie A-9 virus. The death rates on the 5th, 6th and 7th day after infection were 13%, 20% and 36% for the treated, and 34%, 60% and 80% for the controls respectively. At the end of 10 days, the death rate for the treated was 60% and that for the control was 100%. It must be remembered that only a single dose of 2.5 µg of thymus extract was given to each mouse and the thymus extract was prepared from a different species, the calf.

Significance to Bio-medical Research and the Program of the Division. For the first time antiviral substances have been isolated from the thymus gland. Further study might result in some preparation with therapeutic value. It may also be possible to use such material to prevent possible untoward effect following oral live virus vaccine.

Proposed Course of Project: Further chemical purification and identification of the thymus extract and more assay work in mice with viral infections or viral tumors are desired.

Part B included Yes X No___

PHS-NIH
Individual Project Report
Calendar Year 1962

Part B

Honors, Awards and Publications

Publications other than abstracts from this project:

Li, C. P., Prescott, B., and Jahnes, W. G., Antiviral activity of a fraction of abalone juice. Proc. Soc. Exp. Biol. Med., 109: 534-538, 1962.

Li, C. P., Prescott, B., Jahnes, W. G., and Martino, E. C., Antimicrobial agents from mollusks. Trans. New York Acad. Sci., Ser. II, 24: No. 5, 504-509, 1962.

Serial No. DBS 58
1. Laboratory of Virology & Rickettsiology
2. Section on Virus Biology
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A

Project Title: Further Attenuation of Sabin Type III Virus

Principal Investigator: Dr. Chen Pien Li

Other Investigator: Mr. Elmer C. Martino

Cooperating Units: None

Man Years:
Total: 3/4
Professional: 1/4
Other: 1/2

Project Description:

Objectives: The recent field experience with the Sabin III virus has prompted some efforts by the Virus Biology Section to investigate both the practicability of strengthening the stability of the Sabin type III virus and the possibility of isolating a new more stable type III virus.

Methods Employed: We have proceeded upon the premise that the Sabin type III virus (Leon 12 a_1b) may not be fully attenuated. Our experience has shown that avirulent or less virulent variants can usually be obtained when a virulent strain is passed in the presence of an antiviral agent. We used the psoralen drugs throughout this investigation since we have found these drugs possess antiviral activity against the Sabin type III virus. We obtained from Dr. Gerber, a passage in primary vervet monkey kidney cells that was made from the original Sabin type III virus. This same type of cells was used in all the work carried out in this investigation.

We were informed that the first tissue culture passage virus from the original Sabin type III seed was T- and D-. This virus was passed and plaque purified four times. The drug 8-methoxypsoralen was incorporated during one of the plaque passages, into the agar overlay at 50 µg/ml concentration. The virus, thus purified, was then passed consecutively in vervet cell monolayers maintained in Hanks solution with 2% inactivated calf serum. These cells were treated with a mixture of three chemical compounds, namely, khellin, 8-methoxypsoralen and 2', 4, and 8-trimethylpsoralen, all at 10 µg/ml concentration, and the cells were

treated with these drugs both before and after inoculation of virus. Two controls were used. One was the unpurified TC passage virus and the other was the same as the plaque purified virus. These controls were passed in the same way except that the drugs were omitted from the medium.

Major Findings: To date eight passages were made in the presence of the drugs. After the eight passages, the virus was subcultured without the drugs (vk18) and it was found to be T- and D-. At this level the two controls all became T+ and D+. We plan to continue with the study we are now making for further attenuation of this virus and for its characteristics, including its reversibility.

Proposed Course of Project: Efforts to Isolate a New Avirulent Virus. It was noted from the background of the Sabin poliovaccine viruses that a different attenuation process was used for type I than was used for type III virus. The type I virus was passed through monkey testis tissue culture for 34 passages; through monkey skin in vivo (alternating with monkey kidney TC) for 11 passages; through monkey skin grafted on chick embryos for 6 passages. Although there is no definite evidence that the virus multiplied in monkey skin in vivo, it cannot be ruled out completely that there is limited multiplication in a small number of skin cells. When Mahoney virus was inoculated intradermally, the virus was usually found in the local lymph glands. When type III virus (LSc), at the developing stage, was inoculated intradermally, the virus was found in the lymph glands but not as readily or so frequently, as the Mahoney virus. This may indicate that the virus recovered from the inoculated skin is what is left behind, as a less invasive virus while the more invasive ones were carried to the lymph glands. It was noted that the virus in the monkey skin grafted on eggs multiplied to 10^7 ($TCID_{50}$) per ml on each passage when each inoculum was 10^3 or less.

Before Dr. Melnick gave Dr. Sabin the Sabin type III virus, Leon strain, it had 20 passages in monkey brain and 2 passages in monkey testis TC. Dr. Sabin than passed it in monkey kidney tissue cultures for 34 passages before it was triply plaque purified to yield the final seed virus (Leon 12 a_1b). This attenuation process differs in some respects from the attenuation process used to obtain the type I (LSc) virus.

In the early 1950's when the type I poliovirus was being attenuated, we also made some efforts to attenuate the type III poliovirus, Leon strain. Several lines of the Leon virus are now available. They are lines that in the 1950's were passed through mouse spinal cord for 72 passages; through monkey testis tissue culture for 15 passages; through monkey skin, in vivo (alternately with TC), some for 4 and some for 5 passages; in monkey skin grafted on chick embryos, some for 3 and some for 5 passages; and through monkey kidney tissue culture; some for 9, and some for 24 passages. These viruses were stored at -50°C; some on 5/17/55, and some on 8/13/55. They were removed from the freezer on 10/31/62 and were transferred to vervet cell monolayer cultures. Some of these cultures yielded good growth. We are now studying the characteristics of these viruses. It is planned that if the results of the previously described efforts to restablize the Sabin type III virus prove to be satisfactory, further efforts with the new type III virus as a replacement will be discontinued.

Serial No. DBS 59

1. Laboratory of Virology & Rickettsiology
2. Section on Respiratory Viruses
3. Bethesda 14, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A

Project Title: Typhus Vaccine - Killed Epidemic

Principal Investigator: Dr. J. Anthony Morris

The project reported under this title for the years 1960 and 1961 is reported in 1962 under the title of Rickettsial Vaccines.

Serial No. DBS 60

1. Laboratory of Virology & Rickettsiology
2. Section on Respiratory Viruses
3. Bethesda 14, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A

Project Title: SV_{40} Pathogenicity for Man

Principal Investigator: Dr. J. Anthony Morris

Other Investigators: Dr. Joseph F. Fraumeni, Jr. (NCI)

Cooperating Units: Epidemiology Branch, NCI

Man Years: None

Project Description:

As reported in the Annual Report, 1961, the acute phase observations on 35 adult volunteers inoculated by the respiratory route with SV_{40} virus are completed, the findings published, and the medical records deposited in the Medical Record Department, Clinical Center. However, periodic physical and serologic examinations will continue to be made on the four volunteers who are available for followup study; this will be the primary responsibility of Dr. Fraumeni.

Serial No. DBS 61
1. Laboratory of Virology & Rickettsiology
2. Section on Respiratory Viruses
3. Bethesda 14, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A

Project Title: Studies Concerned with Virus Identification

Principal Investigator: Dr. J. Anthony Morris

Other Investigators: Mr. Calvin G. Aulisio
Dr. Bennet L. Elisberg (WRAIR)
Miss Marilyn F. Bozeman (WRAIR)
Dr. William L. Pond (Miami)
Dr. P. A. Webb (USAMRU)

Cooperating Units: WRAIR, Washington, D. C.
University of Miami, Miami, Florida
U.S. Army Medical Research Unit, Malaya

Man Years:
Total: 2/10
Professional: 1/10
Other: 1/10

Project Description:

Coxsackie A4. A virus isolated from the blood of a jaundiced child with fever and rash and with signs and symptoms compatible with a clinical diagnosis of infectious hepatitis was identified as Coxsackie virus, Group A, type 4. Antibodies directed against the recovered virus and against the prototype strain of Coxsackie A4 appeared in the patient's blood during convalescence but not in the blood of any of 54 adults with clinically diagnosed viral hepatitis. While the significance of presence of Coxsackie A4 viremia in a patient with hepatitis is not clear, it seems worthwhile to proceed with studies to determine the frequency with which this virus is encountered in children in association with illnesses clinically diagnosed as infectious hepatitis.

Unidentified hemadsorbing virus. An unidentified hemadsorbing virus was recovered from the visceral tissues of a mouse (Peromyscus leucopus). The new agent, which on the basis of its physical and biologic properties appears to represent a new myxovirus, evoked development of high serum levels of specific neutralizing and CF antibodies when injected into guinea pigs. However, the new virus was not neutralized by antisera prepared against any of the known myxoviruses. The agent grew readily

in embryonated eggs, produced lethal infections following intracerebral injection in white mice and hamsters, and induced degenerative changes in a variety of cultured cells. Neutralizing antibodies against the new virus were not found in the blood of any of 77 wild animals belonging to 10 different species but were found in 7 of 8 pools of serum obtained from the wild mouse, Peromyscus leucopus, and in 7 of 87 human sera in titers ranging from 1:10 to 1:160. Presence in human serum of antibodies directed against the new agent suggests that this virus, or one related to it, is active in the human population.

Significance of the program to the Division. Continued investigation of the identity of viruses recovered from the blood of jaundiced children is expected to contribute to the elucidation of the etiology of the syndrome recognized by the clinician as viral hepatitis. Characterization of new hemadsorption viruses contributes to the solution of one of the many problems associated with this group of agents which have recently been recognized as being of significance in respiratory diseases of man.

Part B included: Yes

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Individual Project Report
Calendar Year 1962

Part B Honors, Awards, and Publications

Publications other than abstracts from this project:

Morris, J. A., Elisberg, B. L., Pond, W. L. and Webb, P. A.: Hepatitis associated with Coxsackie virus Group A, type 4., New Eng. J. Med. 13 Dec. 1962.

Serial No. DBS 62
1. Laboratory of Virology & Rickettsiology
2. Section on Respiratory Viruses
3. Bethesda 14, Md.

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A

Project Title: Studies Concerned with Respiratory Viruses

Principal Investigator: Dr. J. Anthony Morris

Other Investigators: Dr. Motoichi Hatano (visiting scientist)
Mr. Calvin G. Aulisio
Mr. Jack C. Jenkins
Dr. Roslyn Q. Robinson (CDC)

Cooperating Units: Respirovirus Unit, Communicable Disease Center, Atlanta, Georgia

Man Years:
Total: 6-3/5
Professional: 2-3/5
Other: 4

Project Description:

A. Influenza

Objectives: Work on this project was directed toward collection of data which would assist in determining whether a revision of the current influenza virus strain formula would be indicated.

Major Findings. A strains. In the winter of 1961-62, sporadic outbreaks of influenza occurred in Japan, Taiwan and New Zealand, during which a number of Asian strains were isolated by workers in several monitoring laboratories located in these areas. Some of the strains were sent to the Division for antigenic analysis. The results obtained in hemadsorption-inhibition tests performed in cell cultures and in neutralization tests performed in mice, indicated an extensive shift in antigenic composition in some of the 1961-62 Asian strains away from the prototype A2/Japan/305/57 contained in the present vaccine.

B strains. Antigenic analysis of influenza B strains recovered in the winter of 1961-62 in outbreaks of influenza in the United States and Canada indicated a clear, but relatively small antigenic difference between the recent strains and the older strains contained in the current vaccine.

Thus, it appears that a major antigenic change has occurred in recent isolates of A2 viruses and a minor shift in B viruses as compared with strains of previous years. These findings indicate that revision of the strain composition of the influenza vaccine to be used in the winter of 1963-64 should receive careful consideration.

Significance to Program of the Division. Continuous change in antigenic composition of influenza viruses constitutes a basic problem in control of influenza by vaccination and emphasizes the need for maintaining the present program of analyzing strains of viruses recovered during influenza outbreaks and for comparing them with strains employed in licensed influenza vaccine.

B. Adenoviruses

Objectives: The principal effort in this area has been directed toward development of a reliable procedure to measure the potency of adenovirus vaccines.

Major Findings. While little progress has been made in the solution of the difficult problem of developing an improved procedure for measuring the immunizing capacity of the three components in adenovirus vaccine, nevertheless, a number of variables inherent in assay systems employing rabbits or guinea pigs have been defined.

Rabbits. Approximately a quarter of the rabbits available from three different sources, possessed in their sera at the time of arrival at the laboratory, neutralizing antibodies against adenoviruses types 3 and 7. As was to be expected, rabbits with naturally occurring adenovirus antibodies responded in an entirely different manner to inoculation with the test vaccine than did normal rabbits without such antibodies. Rabbits which have been screened and found to be free of adenovirus antibodies appear to be no more valuable in assaying adenovaccine than are guinea pigs. Hence, no additional work with rabbits is contemplated.

Guinea pigs. In guinea pigs it was necessary to give multiple injections of trivalent vaccine to elicit formation of antibodies directed against each of the 3 vaccine components. Injection of a large volume (5 ml) of vaccine on a single occasion resulted in formation of moderate levels of antibodies directed against types 4 and 7, but in development of little or no antibody against type 3. Three injections of trivalent vaccine administered according to the standard assay procedure was followed by high levels of antibodies against types 4 and 7, and a moderate level against type 3.

Proposed Course of This Project. It is hoped that progress in this field might be made by application of a complex hemagglutination technique developed by Drescher for determining the number of viral particles in a given suspension of influenza virus. In the coming year Drescher's procedure will be used in an attempt to measure the number of adenovirus particles in adenovirus vaccines. Until an improved method of assaying potency of adenovirus vaccines is developed, the present procedure based on the antigen extinction principle and the use of guinea pigs will continue.

Part B included Yes____ No__X__

Serial No. DBS 63

1. Laboratory of Virology & Rickettsiology
2. Section on Basic Virology & Rickettsiology
3. Bethesda 14, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A

Project Title: Avian Leukosis Complex

Principal Investigator: Mr. William G. Jahnes

Other Investigators: Mr. William P. Jones
Mr. George E. Grubbs
Miss Elizabeth B. Jackson
Dr. Joseph E. Smadel

Cooperating Units: None

Man Years:
Total: 1½
Professional: 1
Other: ½

Project Description:

Objectives: Development of procedures for detecting the presence of viruses of the avian leukosis complex in viral vaccines prepared for use in man from chick embryo cells in tissue culture or from chick embryo tissue "in ovo."

Methods employed: Modern tissue culture techniques.

Major findings: During the first half of 1962 a task force, drawn from various units in the LVR, established on a working basis at the NIH Rubin's test for detecting the Rous interference factor (RIF) which now appears to be one of the viral agents in the avian leukosis complex. The test is tedious and difficult to perform because of the large number of variables inherent in the technique.

The task force was converted to a permanent group in September and constituted the Avian Leukosis Unit in a newly converted laboratory. The Unit now performs tests for the detection of RIF as part of the biologics control of live attenuated measles virus vaccine. The major difficulty continues to be that of finding a source of chick embryos free of RIF. Hens which have provided eggs free of virus when tested in other laboratories have at times provided eggs which were positive when tested here.

Initial steps have been taken to establish a RIF-free flock of hens at the NIH.

Significance to biomedical research and the program of the Institute: The RIF test is at present the procedure of choice for detecting viruses of the avian leukosis complex and, hence, has an important role in safety testing of vaccines of chick origin.

Proposed course of project: Efforts continue to develop a flock of chickens free of agents of the avian leukosis complex.

Attempts will be made to improve the present RIF test and to find a simpler procedure for the detection of these viruses.

Serial No. DBS 64
1. Laboratory of Virology & Rickettsiology
2. Section on General Virology
3. Bethesda 14, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A

Project Title: Investigations Concerning Measles Virus and Vaccine

Principal Investigator: Dr. Harry M. Meyer, Jr.

Other Investigators: Miss Nancy G. Rogers
Dr. Daniel D. Hostetler, Jr.
Mrs. Barbara B. Jackson
Dr. Ruth L. Kirschstein (LVI, DBS)

Cooperating Units: Department of Pediatrics, Walter Reed General Hospital, Washington, D.C.
Babies Hospital, Columbia-Presbyterian Medical Center, New York, New York
Agency for International Development, Republic of Upper Volta
Laboratory of Viral Immunology, DBS, NIH
Pediatric Metabolism Branch, (NIAID)

Man Years:
Total: 3 3/4
Professional: 1 3/4
Other: 2

Project description:

A. Clinical studies with live measles vaccine. (1) During 1961, normal and debilitated children were vaccinated with a single lot of avianized Edmonston attenuated measles vaccine; some of the children received the vaccine alone, the others were also given measles immune gamma globulin simultaneously. This study on debilitated or "high risk" children is continuing although at a decelerated pace. All children with severe cardiac or fibrocystic disease received both measles vaccine and gamma globulin. The study in normal children has been expanded to determine the feasibility of (a) measles immunization by the percutaneous route and (b) combined measles-smallpox vaccines administered by jet injector, with the possibility of including yellow fever (see Volta I and II studies below).

Eleven susceptible children were immunized with measles vaccine by the multiple pressure method. Only one developed measles antibodies. The remainder were revaccinated by the intramuscular route with subsequent seroconversion.

In developing countries, the need for large scale, single shot, multiple immunization is apparent if not always possible. As a preliminary to the large-scale vaccination program in the Republic of Upper Volta (see Volta II below), 48 normal measles-susceptible American children were immunized as follows, using the jet injector for inoculation: 23 with measles vaccine alone and 25 with mixed measles-smallpox vaccine. Of these children, 40 converted serologically with a fourfold or greater rise in antibody titer as demonstrated in the measles hemagglutination-inhibition (HAI) test. Seven appeared to have had previous experience with the virus (in spite of a negative history) as evidenced by the presence of measles antibody in the preimmunization serum specimen. There was one apparent miss -- a nine-month-old child with "no known exposure to measles or gamma globulin." This child was one of the eight who received primary smallpox vaccination in conjunction with the measles vaccine. Twenty-five children received mixed measles-smallpox vaccine in a single injection. For 8 of these, this constituted primary vaccination, and all developed primary "takes" as well as serological conversion as demonstrated by the smallpox HAI test. For 13 of these children, this constituted a second smallpox vaccination. All except two demonstrated a two-fourfold increase to preexisting smallpox antibody. Two possessed antibody of equal titer in both specimens. The sera of 4 children have not been tested.

(2) Volta I. From November 1961 through January 1962, three members of the LVR visited the Republic of Upper Volta at the invitation of the Ministry of Health to attempt to determine the acceptibility of live measles vaccine in a population suffering from many nutritional, infectious and parasitic maladies. Six hundred and eighty-three (683) children were vaccinated with live attenuated measles virus vaccine (Edmonston strain) donated for this study by Merck, Sharp and Dohme, West Point, Pennsylvania. Most of the children were between the ages of 7 months and 3 years. Blood specimens were obtained from 315 children prior to vaccination and from 217 who returned for examination 4 weeks after vaccination. Vaccinees were divided into three groups of approximately equal size which received vaccine alone, vaccine followed by gamma globulin and gamma globulin alone (controls). Sufficient vaccine was left with the officials of Upper Volta to immunize these controls at the completion of the study. Parents were instructed to return the children to the dispensaries at 2-day intervals for 2 weeks following vaccination. All children with fever or signs and symptoms of illness during this period were examined and treated by the [illegible] team. Antibody studies performed at the NIH established that 94% of the children vaccinated were susceptible to measles and that 100% of those susceptibles who received vaccine subsequently developed detectable antibodies. As was expected, the incidence and severity of vaccine-related febrile reactions and rashes was higher among the group receiving vaccine alone than among those of the group receiving virus subdued by gamma globulin. The clinical reactions closely paralleled those observed in American children. There was no indication that vaccination by either method aggravated pre-existing malnutritional or infectious disease status. It was concluded, therefore, that live attenuated measles vaccine, either with or without gamma globulin, would be well tolerated by this subpar population.

Indeed, the dire need for such vaccination was amply demonstrated by the avidity with which the mothers sought the vaccine on their own initiative.

The need for measles vaccination in Upper Volta is acute (annual outbreaks with up to 25-50% mortality). Conversations of the NIH team with Volta health officials revealed many problems confronting a widespread mass immunization program. As a step toward possible partial solution of the problem of administration of vaccine to several hundred thousand children, five children were vaccinated by the percutaneous route (standard multiple pressure through one drop of vaccine containing approximately 500 $TCID_{50}$ virus). Subsequent serologic studies at the NIH established that one child possessed measles antibodies at the time of vaccination. The other 4 demonstrated an appropriate immune response. This apparently successful small experiment sparked the disappointing study reported in A (1) of this project.

(3) Volta II. Following the successful completion of the Volta I project, and with the enthusiastic cooperation of the Ministry of Health, Upper Volta, and AID/Washington and Abidjan, a two-pronged collaborative measles vaccination program in Upper Volta was launched for the winter of 1962-1963. For this Volta II project, personnel were provided from the LVR, DBS and the Republic of Upper Volta. Part 1 of this study was designed (a) to determine the efficacy of combined measles and smallpox vaccines administered by jet injection, (b) to explore the possibilities of a triple vaccine (measles, smallpox and yellow fever) administered in the same manner, and (c) to test again, in a somewhat larger group of children, the percutaneous route of inoculation for administration of measles vaccine. Preliminary studies in a small number of American children (reported in A (1) of this project report) have demonstrated the safety and efficacy of combined measles-smallpox vaccines administered by the jet injector. Studies in American adults, performed elsewhere, have indicated that smallpox and 17D yellow fever vaccines can be satisfactorily combined in the same injection. No such triple vaccine as proposed for this study has been tested in American children or adults.

Part 2 of the Volta II study was designed as a large-scale, mass immunization program to try to prevent the annual, severe measles outbreak, using a commercially prepared avianized live measles vaccine administered by jet injection. The health Ministry indicated that 100-200,000 children, perhaps more, would participate. The NIH team will train teams of Volta health personnel to use and maintain the jet injection machines and take part in the mass immunization program.

Part 1 of the Volta II project has been completed and Part 2 has been launched. Results of serological studies as well as reports of the overall effectiveness of the mass immunization program will become available during the coming year.

B. Studies directed toward standardization of serological tests for measles. Complement fixation and neutralization tests for the demonstration of antibodies to measles virus have been standardized in this laboratory. These methods were reported at the International Conference on Measles Immunization held at the NIH in the fall of 1961 (see Part B (3)).

Recently, hemagglutination and hemagglutination-inhibition tests with measles virus were described (Peries and Chany, 1960; Rosen, 1961; deMeio, 1961). This test has been under study in the SGV for the past year in comparison with the older serological procedures for the detection of measles antibodies. In brief, the HAI test has proved to be more sensitive than the complement fixation test for use in serological surveys, diagnosis of recent infection and, finally, antibody determinations subsequent to the immunization of children and monkeys with live measles vaccine. In general, the results with the HAI tests are comparable to those obtained with the tissue culture neutralization test although slightly less sensitive with sera containing minimal antibody. This slight disadvantage is probably dependent on mechanical factors, i.e., undiluted sera may be used as the starting point in the neutralization test whereas the lowest dilution attainable in the HAI test is 1:2. In actual practice, HAI tests start at a dilution of 1:8 in the interest of conserving serum. Presently the microtiter technique for performing hemagglutination-inhibition tests is being investigated.

The HAI test possesses the advantages of speed and economy over the more familiar and tedious neutralization test. Although comparative data are insufficient at this time, as more such vaccines are tested it is felt that the HAI test will supplant the neutralization test for use in potency determinations of killed measles vaccines. It is the method of choice for antibody determinations in such studies as are described in Section A (2),(3) of this report.

C. Markers of virulent and attenuated measles virus in rhesus monkeys. Our 1961 annual report described the inoculation of susceptible rhesus monkeys with low passage Edmonston measles virus (virulent) and attenuated measles virus (Edmonston B level live vaccine). Isolation of measles virus from monkeys inoculated with the virulent strain was accomplished with ease from blood, cerebrospinal fluid and swabs from rectum, throat, nasopharynx and conjunctiva as well as urine; no virus was recovered from similar specimens obtained from the animals inoculated with the attenuated strain. Both groups converted serologically. In neither group did the cage and room controls (added to each experiment 48 hours after inoculation) evidence any sign of infection -- clinically, serologically or by virus isolation methods. At necropsy there were no significant findings. The pathological studies were performed by Dr. Kirschstein of the LVI; a complete report is pending.

Inasmuch as the above monkeys were inoculated in the manner prescribed for neurovirulence tests of live measles vaccine (i.e., by central

nervous system routes) a third experiment was initiated to try to explain the failure of the control monkeys to become infected during the first two experiments. Two monkeys were inoculated by the intranasal route with the virulent strain; cage and room controls were introduced 48 hours later. Seroconversion of the inoculated animals was demonstrated by neutralization and HAI tests. There was no serological evidence of infection in the controls.

D. Ecology of measles in monkeys. This portion of the measles project has been concluded. The findings were reported at the International Measles Conference held at the NIH in 1961. (See Part B (1)).

E. Evaluation of potency tests for live measles vaccines. The DBS potency test for live measles vaccine using (Salk) monkey heart (MH) tissue cells has been reported (Part B (2)). During the early spring and summer of 1962, sequential titration of the DBS measles virus reference strain, Lot 1, indicated an alarming drop in the titer of this reagent. Comparative titrations in MH and BS-C-1 cells (continuous green monkey kidney cells derived by Mrs. Hopps, LVR) indicated that this was a function of a failing sensitivity of the MH cells and not a decline of the viral activity of the reference strain. This reference has now been restandardized, using the BS-C-1 cells as the indicator system. It is planned to test this reference in several recently available continuous human diploid cell lines for their possible use in potency tests of live measles vaccines.

Significance to biomedical research and the program of this Division. All work of this Section pertaining to measles is directly concerned with problems of control of measles vaccine as well as its efficacy among peoples of below standard public health conditions.

Proposed course of project. Work will be continued along the lines described.

Part B included: yes

Part B Honors, Awards, and Publications

Publications other than abstracts from this project:

1. Meyer, H. M., Jr., Brooks, B. E., Douglas, R. D., Rogers, N. G.: Ecology of measles in monkeys, Am. J. Dis. Child. 103: 307-313, 1962.

2. Meyer, H. M., Jr., Brooks, B. E., Douglas, R. D., Rogers, N. G.: Potency testing of live measles vaccine, Am. J. Dis. Child. 103: 457-459, 1962.

3. Meyer, H. M., Jr., Brooks, B. E., Douglas, R. D., Rogers, N. G.: Measles serologic standards, Am. J. Dis. Child., 103: 495-502, 1962.

Serial No. DBS 65

1. Laboratory of Virology & Rickettsiology
2. Section on General Virology
3. Bethesda 14, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A

Project Title: Investigations Concerning Vacuolating Virus (SV_{40})

Principal Investigator: Dr. Harry M. Meyer, Jr.

Other Investigators: Miss Nancy G. Rogers
Dr. Daniel D. Hostetler, Jr.
Mrs. Barbara B. Jackson

Cooperating Units: Laboratory of Viral Immunology, DBS

Man Years:
Total: 4 5/6
Professional: 1 3/4
Other: 3 1/6

Project Description:

Ecology of SV_{40} in monkeys. This portion of the project has been concluded. The results are reported in part in the publication listed in Part B of this report.

Pathogenesis of SV_{40}: Studies of the pathogenesis of SV_{40} in susceptible rhesus monkeys have been continued. The experiments were designed to obtain detailed observations over a short period of time in certain of the animals and, in others, extended observations over a year were to be made. The last of the monkeys has just been sacrificed. Information on diagnostic virus isolation tests, serological tests and on the histopathology is still to be completed and analyzed. Many of the findings are similar to those reported earlier in Cercopithecus monkeys. However, a few observations are worth recording at this time. Infected rhesus monkeys shed SV_{40} virus on occasion for as long as four or five months in the throat secretions, urine and feces. Cell cultures prepared from renal and splenic tissues when sacrificed a year after initial infection yielded SV_{40} virus. Histopathological changes in the central nervous system of susceptible rhesus sacrificed about three weeks after intracerebral inoculation with SV_{40} consisted of infiltrations of lymphocytes and mononuclear cells in the ependymal region. SV_{40}-immune monkeys, similarly inoculated, did not display similar lesions.

Significance: SV_{40} continues to be of considerable academic interest to virologists and requires constant vigilance on the part of manufacturer and of the DBS to insure that it is not present in vaccines approved for use in man. The important progress that has been made in the biologics control aspects of SV_{40} is that procedures, practices and techniques have advanced to the point where vaccines can be produced from materials prepared from monkey kidney tissues without contamination with this ubiquitous simian agent.

Part B included: yes

PHS-NIH
Individual Project Report
Calendar Year 1962

Part B Honors, Awards, and Publications

Publications other than abstracts from this project:

Meyer, H. M., Jr., Hopps, H. E., Rogers, N. G., Brooks, B. E., Bernheim, B. C., Jones, W. P., Nisalak, A., Douglas, R. D., Studies on simian virus 40, J.Immunol. 88: 796-805, 1962.

Serial No. DBS-66
1. Laboratory of Biophysics and Biochemistry
2. Research Section
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A

Project Title: Studies of the inactivation of viruses.

Principal Investigators: C. W. Hiatt, Ph.D., Nobuto Yamamoto, Ph.D., and Dorothy Moore, B.A.

Other Investigators: None

Cooperating Units: None

Man Years:
Total: 3.25
Professional: 2.00
Other: 1.25

Project Description:

Objectives: (1) To gain information about the fundamental nature of the various biological properties of viruses through studying the mechanisms of inactivation of these properties by physical and chemical agents.

(2) To develop an understanding of processes of inactivation that may be applied to the preparation of viral vaccines.

Methods Employed: Various animal and bacterial viruses are cultivated in cell cultures and the infective fluids from these subjected to treatment with graded doses of the inactivating agent. Samples taken at the different dosage levels are assayed for infectivity, and the kinetic relationship between dose and survival ratio is established. From the characteristics of the survival curve inferences are drawn about the properties of the virus and the mechanism of the inactivating process.

Major Findings: (1) Photosensitization of poliovirus. Poliovirus sensitized to light by incorporation of proflavine during intracellular maturation has been used as an experimental inoculum for tissue culture cell systems generally regarded as refractory to infection with poliovirus. The cells are disrupted by freezing and thawing at measured time intervals after inoculation. The cell-free supernatant fluids are irradiated with visible light at a dosage level capable of destroying essentially all of the photosensitive virus. Progeny virus is not sensitive to light and survives this treatment. By this procedure it has been possible to find evidence for multiplication of poliovirus, type 1 (Mahoney), in primary rabbit kidney and chick embryo cell cultures and in secondary mouse embryo cell cultures. The yield of new virus is small, and by ordinary techniques would be obscured by surviving parent virus associated with the cells. The tentative conclusion is that several non-primate cell systems contain a small fraction (10^{-5} to 10^{-6}) of cells which are subject to infection.

(2) Photodynamic inactivation of bacteriophages. A study of the mode of action of toluidine blue in sensitizing various phages to light has led to the following conclusions:

(a) T3 coliphage is inactivated by a multi-hit process which indicates that cumulative damage is required for inactivation. A conceptual model of the double-stranded DNA of this phage includes approximately 6 bonds which hold the two DNA strands in alignment. Any one of these 6 bonds is sufficient to maintain integrity of the DNA, but if all 6 are broken, the strands come apart and the information necessary for replication is lost.

(b) T2 and T4 coliphages are inactivated by a single-hit process after a very slow sensitization reaction. The DNA of these phages is known to be double-stranded but relatively labile. We interpret our findings as indicating that the integrity of the DNA of this phage depends upon existence of a single type of bond, possibly between the DNA and an "inner protein". When any bond of this type is broken, the DNA is unprotected and loses its ability to induce replication of the particle.

(c) Strains of RNA phage and single-stranded DNA phage are inactivated by a single-hit process, indicating that dislodging an electron at a single critical point can suffice to destroy replicating ability of the phage nucleic acid.

(3) Theoretical aspects of the kinetics of viral inactivation. A review article comparing the several integrating principles pertaining to viral inactivation kinetics has been prepared and will be submitted for publication.

(4) Photochemical reactions induced by optical masers. A pulsed ruby laser (emission wavelength 6943 A) and a continuous wave gaseous phase Helium-Neon laser (emission wavelength 6328 A) have been tested as energy sources for photodynamic action experiments. Neither of the wavelengths available was effective for inactivation of T3 coliphage sensitized with toluidine blue. It will be necessary to find a dye with an action spectrum more closely matched to the emission band of existing lasers in order to pursue this line of investigation.

Significance to the Program of DBS. The continued investigation of the mode of action of viral inactivating processes is expected to contribute to the fundamental basis for control of viral vaccines.

Proposed Course of Project. This project will be continued.

Part B included Yes /X/ No /__/

Serial No. DBS- 66

PHS-NIH
Individual Project Report
Calendar Year 1962

Part B Honors, Awards, and Publications

Publications other than abstracts from this project:

Hiatt, C. W., Gerber, P., and Friedman, R. M.: Photodynamic inactivation of the vacuolating virus, SV40. Proc. Soc. Exptl. Biol. Med. 109:230-232, 1962.

Hiatt, C. W.: Differential rate methods for selective inactivation of viruses. 7th Int. Cong. on Biol. Standardization, London, 118-127, 1962.

Honors and Awards relating to this project: None

Serial No. DBS- 67
1. Laboratory of Biophysics and Biochemistry
2. Research Section
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A

Project Title: Physical and chemical characterization of viruses.

Principal Investigators: John F. Thiel, B.A., Raoul J. Benoit, Jr., M.S., and Andrew M. Young, M.S.

Other Investigators: Bernice E. Eddy, Ph.D. (OD), Joseph P. O'Malley (LVR), and Ruth L. Kirschstein, M.D. (LVI)

Cooperating Units: Office of the Director, Laboratory of Virology and Rickettsiology, and Laboratory of Viral Immunology, all in Division of Biologics Standards.

Man Years:
Total: 1.50
Professional: 1.50
Other:

Project Description:

Objectives: To obtain information about the physical dimensions and chemical composition of animal viruses and to correlate this information with biological properties.

Methods Employed: Standard methods of physical and chemical analysis, including ultracentrifugation and electron microscopy, are supplemented by specialized techniques for concentrating and purifying viruses.

Major Findings: (1) Electron microscopic observations of simian viruses. Tissue culture cells infected with various members of a group of small viruses of simian origin were submitted for examination by Dr. Eddy (OD). Specimens were pelleted, fixed, embedded, sectioned, and stained prior to examination in the electron microscope. Several of these preparations appeared to have concentrations of small particles not seen in control samples. Proof that these are virus particles awaits the determination of time of highest virus concentration in the tissues and upon more efficient methods of purifying and

concentrating the virus. This will enable the use of more elaborate staining procedures and permit the determination of size and shape of the particles.

(2) Attempts to visualize A-1 virus in the electron microscope. Ten samples of tissue culture or the fluid in which the cultures had been grown were provided by Dr. J. P. O'Malley, LVR. Several of these preparations, when processed, appeared to have concentrations of particles of the estimated size and shape of the A-1 virus. Further work is in progress using techniques of ultracentrifugation and diffusion gradients to obtain a higher concentration of purified virus permitting the use of negative staining techniques and accurate size determinations.

(3) Examination of tumor tissues for presence of virus particles. Samples of tumors from hamsters which had been inoculated with cultures of SV40 were furnished by Dr. Ruth Kirschstein, LVI. Virus aggregates, identified as SV40 were found routinely in properly prepared and stained samples. The relative ease with which these infected cells can be found provides a useful tool for the study of these tumors.

Significance to the Program of DBS. Physical and chemical characterization of viruses used for vaccine production and of the adventitious agents which may occur as contaminants is directly related to the control of viral vaccines.

Proposed Course of Project. This project will be continued.

Part B included Yes /__/ No /X/

Serial No. DBS- 68
1. Laboratory of Biophysics and Biochemistry
2. Research Section
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A

Project Title: Attempts to cultivate animal viruses in bacterial cells.

Principal Investigators: Jerome J. Helprin, Ph.D.

Other Investigators: None

Cooperating Units: Section on Respiratory Viruses, LVR

Man Years:
Total: 0.50
Professional: 0.50
Other: 0

Project Description:

Objectives: To determine the feasibility of culturing animal viruses in bacterial cells.

Methods Employed: Cell walls are removed from various species of bacteria by treating the bacteria with lysozyme. Suspensions of the remainder of the cells (protoplasts) are inoculated with virus and subsequently examined for evidence that they have been infected by the virus.

Major Findings: Reproducibility of these protoplast preparations depends upon the time and temperature of incubation of the cells in the presence of lysozyme. These conditions vary with the bacterial genus employed, and have been determined for several genera. In addition to Aerobacter aerogenes, whose protoplasts had previously been shown to adsorb influenza virus, protoplasts have been prepared from Escherichia coli and Salmonella paratyphi. Influenza virus has been added to these protoplasts, and infectivity, in addition to adsorption, will be measured in the absence of active extracellular virus by standard techniques.

Significance to the Program of DBS. The significance of this work to the program of the Division of Biologics Standards lies in the development of simpler methods for the propagation of viruses, which could be of value in both the preparation and testing of virus vaccines. Methods employing normal animal tissues for the growth of viruses have disadvantages which range from the presence of viruses potentially pathogenic for man to the technical problems inherent in the cultivation of animal tissues *in vitro*. If it can be demonstrated that an animal virus can be grown in a bacterial cell, then many of the disadvantages of animal tissue culture could be avoided.

Proposed Course of Project. Project to be continued.

Part B included Yes / / No /X/

Serial No. DBS- 69
1. Laboratory of Biophysics and Biochemistry
2. Research Section
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A

Project Title: Simian virus 40. Electron microscopic studies of its relationship to rhesus kidney tissue culture cells.

Principal Investigators: John M. Easton, M. D.

Other Investigators: None

Cooperating Units: None

Man Years:
Total: 0.33
Professional: 0.33
Other: None

Project Description:

Objectives: To study the interrelationship between SV-40 and the rhesus kidney tissue culture cells in which it grows, using the electron microscope in addition to conventional tissue culture methods.

Methods Employed: The electron microscope is used to examine both naturally and artificially infected rhesus cell cultures, in an attempt to find viral particles in infected cells. Ferritin-labelled antibody is used as a tool for the precise localization of SV-40 viral antigens. Various modifications in the cell-virus environment, such as incubation at suboptimal temperatures, irradiation, and prolonged incubation, are studied in relationship to their ability to influence the yield and cytopathic effect of SV-40.

Major Findings: Electron micrographs of both artificially and naturally infected cultures reveal intranuclear particles, approximately 300 A in diameter, in a fraction of the infected cells. These particles correspond, in shape and location, to descriptions of SV-40 in vervet monkey kidney cells by other investigators. Results to date also indicate that tissue cultures artificially infected with SV-40 do not survive for as long a time as uninfected control cultures.

Significance to the Program of DBS. This study will result in information which may be of assistance in the control of viral vaccines.

Proposed Course of Project. Project to be continued.

Part B included Yes /__/ No /X/

Serial No. DBS 70
1. Laboratory of Blood & Blood Products
2. Blood & Blood Derivatives, Diagnostic Reagents
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A.

Project Title: Development and Application of Control Procedures for Blood and Blood Products.

Principal Investigator: Dr. John T. Tripp

Other Investigators: Dr. David L. Aronson
Dr. J. N. Ashworth
Miss Joan F. Bennett
Miss Marietta Carr
Mrs. Rita Conroy
Miss Ann L. Dayton
Mrs. Eleanor G. Morrison
Mr. Robert C. Scheno
Mrs. Donna C. Williams

Cooperating Units: None

Man Years:
Total: 2.5
Professional: 1.5
Other: 1.0

Patient Days: None

Project Description:

Objectives: To develop improved control procedures and standards by evaluating present control procedures and manufacturing methods as these affect the safety, purity and potency of biological products derived from blood.

Methods Employed: (a) Samples of biological products derived from blood are sent as unknowns to manufacturers or blood banks for comparative testing to check new methods and reagents as well as standard techniques currently in use.

(b) Colored photographic slides of agglutination reactions are interpreted on a voluntary basis by blood bank technicians as a study of blood banking errors. The technicians record their results in different ways, utilizing forms supplied by this Laboratory as well as on the routine forms used in their laboratory.

(c) Various methods of preparing the site of phlebotomy are being studied as part of a continuing investigation of possible causes of bacterial contamination in bank blood.

(d) Containers for the shipment of blood and other products requiring continuous storage at uniform low temperatures are being investigated as to their efficiency and usefulness in this important aspect of the preservation of biologicals. Information is obtained under static laboratory conditions as well as during actual shipment.

(e) Infrared spectrometry is being utilized to determine changes occurring in plastic blood containers resulting from age, temperature and humidity.

(f) The technique of immunoelectrophoresis is being modified and developed to increase the usefulness of this important method in the study of antibody-antigen proteins.

(g) The mechanism of action, the standardization and the clinical significance of tests utilizing "broad spectrum" and "non-gamma" anti-human serum reagents are being studied.

(h) Red blood cells are being used as a model system in a study of methods of drying labile biological materials. Liquid nitrogen is being investigated as a freezing and storage medium to determine the effects of this low temperature on measurable characteristics.

(i) Physical, chemical and serological tests, not routinely performed, are being adapted and applied to whole blood, red blood cells and fresh plasma in a study to develop new control tests for these products for incorporation into regulatory standards.

Major Findings: The various methods and procedures listed above, which describe the areas of interest of this Laboratory in investigations of control procedures, have received only minimal attention during this year. Activities concerned with the investigation of possible violations of the Public Health Service Act have not allowed staff to devote any significant amount of time to these research interests. As a result, there are no results to report.

Significance of Research:

Control procedures of greater significance and specificity can result from investigations such as those carried out as part of this project.

Proposed Course of Project:

As enforcement activities lessen, the various parts of this project will be continued.

Part B included Yes /X/ No / /

Serial No. DBS 70

PHS-NIH
Individual Project Report
Calendar Year 1962

Part B. Honors, Awards and Publications

Publications other than abstracts from this project:

Yokoyama, M., Finlayson, J. S., Solomon, J., Morrison, E. G. Reactions of Rh-Positive Red Cells with Anti-Rh Sera and with Rh Antibody Fractions Separated on DEAE-Cellulose Transfusion, 2, 155-162, 1962.

Bronson, W. R., McGinniss, M. H. The Preservation of Red Blood Cell Agglutinogens in Liquid Nitrogen: Comparative Study of a Technique Suitable for Routine Blood Banking. Blood, 20, 478-484, 1962.

Schmidt, P. J., Morrison, E. G., Shohl, J. The Antigenicity of the $Rh_o(D^u)$ Blood Factor. Blood 20, 196-201, 1962.

Shohl, J., Morrison, E. G., Fahey, J., Schmidt, P. J. Relation of Isohemagglutinin Levels of Gamma Globulin Changes in Disease. The Journal of Laboratory and Clinical Medicine 59, 753-759, 1962.

Kevy, S., Schmidt, P. J., McGinniss, M., Workman, W. G. Febrile, Nonhemolytic Transfusion Reactions and the Limited Role of Leukoagglutinins in their Etiology. Transfusion 2, 7-16, 1962.

Serial No. DBS 71
1. Laboratory of Blood & Blood Products
2. Blood & Blood Derivatives
   Coagulation
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A.

Project Title: Preparation, Characterization, Stability and Potency of Blood Products.

Principal Investigator: Dr. John T. Tripp

Other Investigators: Dr. David L. Aronson
Dr. J. N. Ashworth
Miss Ann L. Dayton
Mr. Paul O. Fehnel
Dr. John S. Finlayson
Dr. Edward H. Mealey
Dr. Michael W. Mosesson

Cooperating Units: None

Man Years:
Total: 5.3
Professional: 3.8
Other: 1.5

Patient Days: None

Project Description:

Objectives: To determine the properties of native blood proteins and to investigate the changes occurring in the physical and chemical properties of these proteins resulting from processing and aging. The mechanisms of these changes are also of interest.

Methods Employed: (a) Parallel samples of liquid and dried Normal Serum Albumin (Human) are stored at 32°C., 5°C. and ambient room temperature. At regular intervals, the samples are tested for stability by viscosity determinations, ultracentrifugation, electrophoresis and nephelometry. During this year similar studies were started on gamma globulin, dextran and PVP.

(b) Samples of liquid plasma in plastic and glass containers are stored at 30°-32°C. At regular intervals the samples are tested for dehydration and sterility. The stability of the samples is determined by ultracentrifugal, electrophoretic, serologic and immunochemical determinations.

(c) In order to characterize and purify the coagulation components and the components of the fibrinolytic system, the techniques of fractional precipitation and column chromatography have been utilized. Efforts have also been directed at the stabilization of these somewhat labile compounds by various enzyme inhibitors.

(d) Test systems useful for estimation of purity of coagulation components have been investigated. Ultracentrifugation and electrophoresis in various media have been employed. N-terminal amino acid determinations have been used as an ancillary method.

(e) There is evidence that formed elements and other components of blood can be separated in a completely closed system by use of high intensity magnetic fields. The design and operation of equipment to separate red cells, platelets and plasma by magneto-electrophoresis is being investigated.

Major Findings: (a) This has been the eighth year of the stability study of albumin. Though prevented by enforcement activities from carrying out the planned amount of work, staff was able to perform enough measurements to confirm previous observations that small but definite changes occur in physical properties of albumin stored at temperatures over 5°C.

(b) The new study on the effect of storage and type of plasma container has recently been initiated. Early observations show that plasma stored in plastic containers undergoes dehydration. The precipitate which forms during storage appears to be different in plasma stored in plastic as compared with plasma stored in glass.

(c) Chromatography of purified human fibrinogen yields two peaks of clottable protein. Despite a high degree of clottability there are still contaminants of fibrin stabilizing factor and an inhibitor of plasmin digestion

(d) Prothrombin seems to exist in at least three forms, two of which are derivatives of the original material isolated from plasma. The conversion of the "native" prothrombin seems to involve at least two steps.

(e) Lack of time has prevented further investigation this year of magneto-electrophoresis.

Significance of Research:

All blood and blood products controlled by the Division of Biologics Standards are required to be stable and potent. Improved methods for the evaluation and assay of these characteristics in vitro increase our ability to determine stability and potency and to place these control functions on a foundation based on fundamental knowledge of the properties of these products.

Proposed Course of Project:

The various parts of this project will be continued.

Part B included Yes /X/ No / /

PHS-NIH
Individual Project Report
Calendar Year 1962

Part B. Honors, Awards and Publications

Publications other than abstracts from this project:

Mosesson, M. W. The Preparation of Human Fibrinogen Free of Plasminogen. Biochim. Biophys. Acta. 57, 204-213, 1962.

Aronson, D. L. N-Terminal Amino Acids Formed During the Activation of Prothrombin. Nature. 194, 475-476, 1962.

Aronson, D. L. and Preiss, J. W. Molecular Weights of Human Prothrombin and Thrombin by Electron Irradiation. Radiation Research 16, 138-143, 1962.

REPORT ON OTHER THAN RESEARCH OR CLINICAL ACTIVITIES OF LABORATORY OF BLOOD & BLOOD PRODUCTS FOR 1962

In addition to the research activities outlined in the accompanying reports, designed to complement and support control functions, the Laboratory of Blood and Blood Products has carried out its primary function of controlling the safety, purity and potency of blood and blood products. Chief among these control functions are the following.

1. As required by regulations, each establishment producing blood products was inspected at least once during the fiscal year. During the year, there have been 10 qualified inspectors available to perform this work in addition to their other duties. In fiscal 1962, the qualified inspectors performed a total of 244 inspections requiring 270 man days on travel status. The investigation of possible violations of the Public Health Service Act, started in the last quarter of 1961, continued through this year. The cases resulting from the investigation are now awaiting trial, but considerable staff time is still required in assisting the U. S. Attorney in preparing the prosecution. It is estimated that 1,500 man days were utilized during 1962 on the investigation with approximately half of this time being on travel status. This extraordinary drain of staff time resulted in the cancellation of inspections of some locations of licensed establishments. Thus it was not possible to inspect most of the donor centers operated by licensed blood banks.

2. Control testing has been carried out on the various blood and blood products produced by 160 licensees operating 233 principle locations and 226 donor centers and other subsidiary facilities. These licensees hold 683 product licenses for blood and blood products. This control testing includes all of the physical, chemical, immunological and related testing found necessary for action on the various blood products submitted for licensure or release or as the result of inspections. In 1962 control testing involved over 2100 lots of blood products including 890 inspection samples. In excess of 12,000 tests were performed on these products.

3. License applications for 70 blood products were reviewed and the licenses were granted. Nine licenses were granted for establishments to produce blood and blood products. There are 10 licenses pending.

4. Labels and circulars were reviewed for all biological products from licensed manufacturers. Over 500 groups of labels and circulars were received and reviewed for compliance with the regulations. This work involved the labels and circulars from the currently 201 licensed establishments which are licensed for 286 different biological products and who hold 1,227 active product licenses each having its own labels.

5. Reference standards are maintained for 7 blood products. Work was continued on 10 new preparations for ultimate adoption.

6. The preparation of regulations and standards for the control of blood products has continued. A draft of Additional Standards for Immune Globulin (Human), Measles Immune Globulin (Human) and Poliomyelitis Immune Globulin (Human) was circulated for comment before preparation of a Notice of Rule Making. Comments received on a draft of Additional Standards for Plasma (Human) have been reviewed for preparation of a further draft.

7. The Blood Bank Section, which serves the needs of patients in the Clinical Center, was transferred early in the year to the Clinical Pathology Department of the Clinical Center.

8 A panel of typed donors among NIH employees was maintained as a valuable resource as a source of extensively characterized red cells for use in the control and research program of the Laboratory. At present, there are 500 employees listed on the panel which is utilized at least weekly.

Annual Report of Activities
Division of General Medical Sciences
Calendar Year 1962

SUMMARY STATEMENT

During the past year, the Division of General Medical Sciences has undergone major organizational changes in conjunction with the establishment of the Division of Research Facilities and Resources and Presidential and Congressional authorization for the establishment of the National Institute of General Medical Sciences and the National Institute of Child Health and Human Development.

The Division was set up in 1958 to encourage and support noncategorical research in the sciences basic to medicine and biology and in certain clinical areas through research grants and research training grants and by means of fellowships to individuals for general research training. Its appropriations have grown from $26,738,000 in FY 1959 to $155,526,000 in the current fiscal year ('63).

The Division is responsible for administering the noncategorical research grants, training grants, traineeships and fellowships in the health sciences of NIH. It also directs the Center for Research in Child Health and the Center for Aging Research.

Clinton C. Powell, M.D., directs the Division as Chief since the retirement of G. Halsey Hunt, M.D., in July. Gordon H. Seger, Dr. P.H., assists Dr. Powell as Associate Chief replacing Frederick L. Stone, Ph.D., who heads the new Division of Research Facilities and Resources.

Budget

The following table summarizes the growth in the appropriations for the Division over the past three years:

	F.Y. 1961	F.Y. 1962	F.Y. 1963
Research Grants	$37,143,000	$ 51,747,000	$ 67,921,000
Training Grants	27,000,000	31,000,000	35,442,000
Research Fellowships	10,000,000	11,290,000	14,480,000
Review and Approval	1,687,000	2,560,000	2,917,000
Administration		490,000	1,266,000
General Clinical Research Centers	5,000,000	27,500,000	33,500,000
	$80,930,000	$124,587,000	$155,526,000

PERSONNEL

At the end of Calendar Year 1961, there were 118 persons in DGMS. At the end of Calendar Year 1962, there were 132 persons, assigned as follows:

Office of the Chief	5
Administrative	13
Information	7
Program Planning and Evaluation	7
Research Training Branch	49
Research Grants Branch	33
Center for Aging Research	4
Center for Research in Child Health	14
Total	132

Major Personnel Additions

Murray Aborn, Ph.D., Executive Secretary Behavioral Sciences Training Committee Acting - Pharmacology and Anesthesiology
Research Training Branch

Donald Beauchamp, Budget Officer
Division of General Medical Sciences

Gerald Atchison, Budget Officer
Center for Research in Child Health

Paul W. Bowman, Ph.D., Scientist Administrator
Research Grants Branch

Eugene Byrd, Ph.D., Acting Director
Center for Aging Research

James W. Dow, M.D., Executive Secretary - Physiology and Biomedical Engineering Training Committee
Research Training Branch

Elizabeth Eberhard, Technical Publications Editor
Information Office
Division of General Medical Sciences

Morris Feitel, M.D., Medical Officer (Pediatric)
Center for Research in Child Health

Lillian Freedman, Research Program Analyst
Center for Research in Child Health

Norman Forbes Gerrie, D.D.S., Program Planning Officer
Chief Dental Consultant
Center for Research in Child Health

*Lillian Gluckman, Acting Information Officer
Division of General Medical Sciences

Donald R. Goldthorpe, Information Officer
Division of General Medical Sciences

John Haje, Financial Analysis Officer
Research Grants Branch

Donald Harting, M.D., M.P.H., Director
Center for Research in Child Health

**Edwin L. Hove, Ph.D., Scientist Administrator
Research Grants Branch

Helen Johns Ossofsky, M.D., Pediatric Consultant
Center for Research in Child Health

Clinton C. Powell, M.D., Chief
Division of General Medical Sciences

Solomon Schneyer, Ph.D., Scientist Administrator
Office of the Chief

Harvey I. Scudder, Ph.D., Scientist Director
Chief, Research Training Branch

Gordon H. Seger, Dr. P.H., Associate Chief
Division of General Medical Sciences

Bernard Shacter, Ph.D., Scientist Administrator
Research Grants Branch

Clair R. Spealman, Ph.D., Scientist Administrator
Research Grants Branch

Gene A. Ward, M.D.
Staff Assistant to the Director
Center for Research in Child Health

*Transferred as Information Officer, National Institute of Dental Research
**Transferred to Food and Drug Administration in November

RESEARCH GRANTS BRANCH

The Research Grants Branch of the Division of General Medical Sciences is supporting research in the basic biomedical sciences. The present trend is toward multidisciplinary studies, in which different techniques and approaches can be applied to the solution of specific problems. The biomedical research supported by the DGMS may be considered under the following broad categories:

Basic Biological Sciences, include investigations into various phases of cell

biology, genetics, embryology and development, physiology, metabolism, nutrition, radiobiology, and microbiology. About 600 research grants, representing about 34 percent of the total number and approximately 28 percent of the total funds, were awarded in this area. The average amount of these grants was $21,718.

Chemistry of Life Processes, includes biochemistry, biophysical chemistry, biophysics, physiological chemistry, medicinal chemistry, pharmacology and toxicology.

The work includes synthesis of new compounds of probable biological activity, of naturally occurring organic compounds to make them more easily available for study, and of analogs of compounds of known biological activity which can be used in research designed to elucidate the relationships between structure and function. Testing programs for determining the properties of these new compounds as possible pesticides or as drugs adaptable to therapy are being developed. More research of this nature is indicated, as the production of new drugs appears to be exceeding present capacity for adequate testing.

Various physical techniques are being adapted to the study of the structure of molecules and the realtionship of structure to physiological function. There is a need for compounds of limited stability for use as fungicides and insecticides and for compounds which will have a deleterious effect upon abnormal cells without harming or disturbing normal cells. About 760 research grants, which represent approximately 43 percent of the total number and 34 percent of the total funds expended, were awarded in this area. The average amount of these grants was $21,206.

Clinical Sciences.

This area includes studies in anesthesiology, dermatology, endocrinology, hematology, obstetrics and gynecology, pathology, surgery, and general medicine. Some basic work in these fields is also included among the biological sciences. About 8 percent of the total number of grants, approximately 145, and about 11 percent of the total funds, were awarded in this area. The average amount was $33,805.

Public Health Research.

This area encompasses research projects which are not specifically disease-oriented, including group and field studies to determine the effectiveness of therapeutic measures,the development of effective epidemiological methods, and study and evaluation of public health practices. Over 3 percent of the total grants, numbering about 60, and about 5 percent of the total funds, were expended in this area. The average amount of these grants was $44,046.

Nursing Research.

This area includes studies in hospital organization and management as they affect nurses, relation of nurse to patient, effectiveness of established

nursing practices, and improvements in the use of nurses. In this field about 50 grants, constituting approximately 3 percent of the total number and expending about 3 percent of the total funds,were awarded. The average size of these grants was $27,944.

Methods and Tools of Science.

In this area are included both the development of coding technics and the application of computer methods to the solution of biological problems ranging from the analysis of electrocardiograms to the determination of molecular structure by the analysis of x-ray crystallographic studies; the development of a sensitive, high-speed cell scanner and counter, and new technics for the analysis of various kinds of data and processes. Work of this kind is difficult to define categorically because it develops in various situations in response to a need. About 84 grants, comprising approximately 5 percent of the total number and about 15 percent of the total funds, were awarded in this area. The average amount ($81,384) of the grants is quite large, because of the size of the investments in computer systems.

Less than 3 percent, or 41, of the Division's grants were awarded for the support of conferences and the publication of material, for the purpose of contributing to the development and dissemination of knowledge.

In some very important areas basic to medicine and biology, large-scale grants to institutions for the support of broadly-based and usually long-term programs of research activity are supported by this Division. Support during the past year included a study of the adaptation of man and animal to arctic conditions, biophysical studies on viral structure and function, programs on developmental biology and pathology, biomedical engineering studies, a program on reproduction in primates and other mammals, and studies of the structure, function and biosynthesis of macromolecules. There were 14 of these grants in excess of $100,000 supported in Calendar Year 1962 representing less than three precent of the total number and (because of their size) about 13 percent of the total funds.

About 85 percent of the Division's grants were awarded to educational institutions of various kinds, with the remaining 15 percent going to research foundations and institutes not associated with educational institutions.

Administrative responsibility for the programs in the General Research Support Grants, the General Clinical Research Centers, and the Special Research Resource Centers has been transferred from the DGMS to the newly established Division of Research Facilities and Resources.

Progress Made in Program Areas

In the area of the basic biological sciences some progress has been made toward increased knowledge of the causes of rejection of tissues and organ transplants in both animal and man, bringing nearer the possibility of success in such operations.

This area is being supported by continuing studies on the physiology of the skin, regenerating systems and differentation, preservation of tissues by freezing, the mechanisms of protoplasmic movement, and a multifaceted approach to unanswered questions on cell division and growth.

Support is increasing for research on reproduction. Projects receiving support are concerned with the structural, chemical, regulatory and functional aspects of the processes by which a living organism begins with the fertilized egg.

By analyzing the chemistry of cervical mucus in both sterile and fertile women, grantees have been seeking answers to problems on reproductive incompatibility of apparently normal and healthy individuals. This, along with studies on the embryological development of animals and humans from conception to birth, is providing increased knowledge of the physiological changes in the mother and is supplying insight into the effects of drugs employed during pregnancy. The stages at which the effects of various internal and external disturbing factors are at their maximum are also being determined.

In other studies, a grant-supported investigator has been able to isolate "promine," containing a growth-promoter and a sterilization factor, from the thymus gland of calves. This finding has an important bearing both on cancer research and the developmental sciences.

Considerable work in genetics is being supported. Little known disorders resulting from genetically controlled disturbances are being recognized and their causes and mechanisms are being elucidated. The study of the nature and distribution of gamma globulin factors is regarded as a meritorius program; the study of human chromosomes is expanding; and an ingenious hypothesis concerning the relation of the sex chromosomes to the autosomes is being investigated.

Preliminary results from work on muscle swelling in old and young has shown that removal of magnesium ions increases muscle swelling, whereas its addition inhibits swelling. The cause-effect implications of this finding are not, as yet, exactly clear, but the study may help explain the loss of muscle strength in old age.

It has been learned that various abnormal conditions such as mongolism, leukemia, and sexual and mental abnormalities are definitely associated with recognizable changes in chromosomes.

Studies are being conducted on the anatomy and physiology of various animals not generally used in biomedical research to find new species in which reactions to certain drugs and conditions will more closely approximate those in humans. Examples are physiological and biochemical analyses of dormancy in the brine shrimp to study its causes and conditions, of temperature regulation in the bat during hibernation, of endocrine production in finches, and of the rhythmic gastric secretion and production of liver glycogen in the frog.

The biophysics and biophysical chemistry programs supported by the Division have more than doubled in the past year. In the area of chemistry of life processes, many new compounds have been synthesized, both for their possible use as pesticides of various kinds and their therapeutic value, as well as for study of the relation of structure and function.

During the past year, the first total synthesis of an antibiotic of the tetracyline group was achieved by a grantee--an accomplishment which may lead to the development of greatly improved antibiotics. Support was also provided for studies on the mechanism of enzyme-substrate complex formation, investigations of the electron interactions between nucleic acids and proteins, the configuration of biological macromolecules, the theory of polymers, and virus structure and function.

There is good evidence that the use of animal serum can be helpful in the neutralization of poisons. A new enzyme test has been developed that permits diagnosis of the rare glycogen storage diseases. Other work has shown that the destruction of various bacteria, both in test tubes and in some humans, may be more effective when both penicillin and streptomycin are used than when either is used alone.

The emphasis in the biological problems has been on the multidisciplinary approach, resulting in considerable progress being made through the award of program-project grants toward an integrated knowledge, at the molecular level, of macromolecular structure and the chemical interrelationships of cellular elements.

These cooperative efforts are also producing better understanding of the mechanisms by which biologically active compounds exert their effects, including the mechanisms of toxicity. Grantees have recently been able to come closer to finding the forces and processes involved in cell division. They have been able to break the cell membrane, disperse the cell content, and leave the mitotic apparatus not only intact but looking as it does in the living cell.

At the molecular level, studies of the nucleic acids are revealing the nature of mutations, DNA-RNA relationships, and the nature and function of the working mechanisms.

In the clinical sciences, the use of new instruments and physical and chemical approaches to current problems are making the efforts of physicians more effective.

Support has been expanded in the field of x-ray crystallography, a productive new method for the study of the three-dimensional structure of biologically active organic compounds. As evidence of the importance of this technique, a Nobel prize for 1962 was awarded to two English workers for their x-ray crystallographic investigations of hemoglobin and myoglobin.

Increasing use of radioactive isotopes has led to more accurate localization of tumors. Ultrasonic methods of cell disintegration are being improved, as are microscopes which permit flying-spot scanning, enabling investigators to

study and measure activities within living cells without having to kill or disrupt them. The application of engineering principles to surgery and to the design of prosthetic devices is resulting in more effective rehabilitation of amputees.

Essentially the same activities will continue to be supported during the next year, with increasing emphasis on interdisciplinary studies.

In the field of public health, research is directed primarily toward studies of the effectiveness of therapeutic measures, epidemiological methods and public health practices.

In the field of nursing, the studies are directed toward an analysis of existing methods as to their effectiveness, nurse-patient relationships, and adoption of more effective practices.

In the development of new techniques and instrumentation, the application of computer methods to biomedical problems has progressed to the stage where analyses can be made by relating the medical history and symptoms of the patient to the background of the basic data which has been put into the computer. Advances in this field, however, are sometimes difficult to communicate adequately. In some cases, for example, innovations may result from investigators attacking a problem with the old methods, and in the course of their work finding new and better ones. Such developments usually result from attempts to produce results which could not formerly be attained by existing methods.

The rapidly increasing size of research grant activities and complexity of administration have made necessary a study of our operations to determine how best to select and code grants information so such data can be retrieved and used in a continuing analyses of the Division's grants programs.

Such data retrieval, might show, for example, the extent to which grants in the genetics area are devoted to human genetics, and the extent to which chemical compounds now derived from natural sources are being synthesized to increase the available supply or modify their action.

Methods are being developed by which better analyses of our activities can be made and information provided as to support in specific areas, on the basis of which trends can be recognized and increased emphasis placed where it is most needed.

It is difficult to get a reasonably accurate picture from the old data retrieval methods. An increase in both the senior and junior staff members is needed to allow time for more thoughtful consideration of this problem, which will continue to increase in size and complexity far more rapidly than the number of persons available to cope with them.

GENERAL MEDICAL RESEARCH PROGRAM-PROJECT COMMITTEE

The General Medical Research Program-Project Committee was transferred to this Division from the Division of Research Grants in November of the past year.

The Division, as of December 31, 1962, was supporting program-projects at nine institutions in seven states at a level of more than two and one-half million dollars.

Operating in the areas of general science basic to medicine and biology, the Committee reviews and recommends for approval or disapproval large-scale grants to institutions for the support of broadly-based and usually long-term programs of research activity.

Dr. Clair R. Spealman transferred from DRG to the program and is the Executive Secretary of the Committee.

PROGRAM PLANNING AND EVALUATION

It has become necessary, because of the breadth and scope of the Division's program to establish formal procedures and more adequate machinery for the continuous review of ongoing programs.

In October of Calendar Year 1962, in order to implement this purpose, the Division began preparations for the establishment of a Program Analysis Branch which will be charged with responsibilities for the collecting, analyzing and dissemination of program data to be used in program evaluation and planning.

The Branch, to be comprised of a Program Analysis Section and a Program Service Section, will be under the direction of Mr. Maurice Odoroff, presently Assistant to the Chief of the Division.

INFORMATION OFFICE

The Information Office, established in the Office of the Chief, is responsible for the organization, planning and distribution of public and professional information programs in accordance with the activities of the Division.

The various activities of the Information Office include the preparation and distribution of information publications, such as pamphlets and brochures on Division programs; issuance of press releases and announcements on large grant awards, personnel appointments, and other items of interest; planning, developing and handling of exhibits and other audio-visual materials; preparation of weekly reports on grantee research accomplishments and others as needed; research and preparation of speeches; and compilation of monthly list of grantee publications.

The Office prepares the opening statement, special reports and other requested material on budget for use by the Division Chief at Congressional Appropriations Hearings.

The Office reviews scientific literature for articles on grantee work and maintains a library of current scientific, lay and professional publications for use by the Division staff.

GENERAL RESEARCH SUPPORT GRANTS PROGRAM

The General Research Support Grants Program, originated in 1961 as an effort to meet the imbalance in the total health related research and research training programs of institutions, in July of Calendar Year of 1962 was transferred to the Division of Research Facilities and Resources.

At the end of Fiscal Year 1962 programs were being supported in 86 medical schools, 49 dental schools, 12 schools of Public Health and 12 schools of osteopathy at a level of $20 million.

GENERAL CLINICAL RESEARCH CENTERS PROGRAM

Administrative responsibility for the General Clinical Research Centers Program was transferred to the newly established Division of Research Facilities and Resources on July 15, 1962. The appropriation for this program was $27,500,000 for Fiscal Year 1962. As of the date of transfer, there were 56 awards to 50 institutions in 26 states, the District of Columbia and Puerto Rico.

SPECIAL RESEARCH RESOURCES BRANCH

In Fiscal Year 1962 $5 million was appropriated by Congress for the support of facilities for computing and data processing, for development of electronic and other instrumentation and for other specialized services in support of institutional research programs. Administrative responsibility for this appropriation, which was increased to $6 million for Fiscal Year 1963, was transferred to the Division of Research Facilities and Resources on July 15, 1962. This transfer included 17 computer centers and one biomedical engineering program.

CENTER FOR AGING RESEARCH

The Center for Aging Research serves as the focal point in the National Institutes of Health for research in aging. The Center stimulates and assists the development of new research projects in gerontology at universities, medical centers, and various other research institutions in this country and abroad; maintains liaison with the NIH intramural and extramural programs, with other bureaus and divisions of the Department of Health, Education, and Welfare and with other Federal agencies and organizations supporting programs in aging; fosters the training of additional research personnel and collects and disseminates data related to research in aging. Through its review of grant applications to the NIH and annual tabulations of active research projects, the Center functions to point up areas in the field of gerontology needing new or additional emphasis.

Changes in professional staff and plans to incorporate the functions of the Center into the proposed National Institute of Child Health and Human Development resulted in a re-evaluation of the Center's activities. Professional staff participated in the evaluation of several of the large aging center programs which have completed several years of operation. These Centers, previously supported by more than one Institute, have been transferred to the DGMS for grant stewardship.

Major emphasis during the past year has been on stimulating new projects for aging research, and on collecting and disseminating data related to aging. A comparison of the number of grants for extramural projects primarily related to aging for the 6-year period ending January 31, 1963 reflects the activity in this area:

	Number of Grants
January 31, 1958	131
January 31, 1959	197
January 31, 1960	244
January 31, 1961	245
January 31, 1962	306
January 31, 1963	345

Collection and dissemination of information related to aging research has continued. The three annual publications "Activities of the NIH in the Field of Gerontology," "Research Programs in Aging," and "Research Highlights in Aging" were distributed widely to scientists concerned with gerontology. In addition, two translations of Russian gerontological literature were published and distributed through the Center. These were "Aging of the Organism at the Molecular Level" by Zh. Medvedev of Timiriasev Agricultural Academy, and "Second Conference on Gerontology and Geriatrics, Moscow 1960."

Authorization to establish a new National Institute of Child Health and Human Development was passed by the 87th Congress and signed by the President. The program of this new Institute is expected to include research and training in the biological, medical, and behavioral aspects of aging and will incorporate the functions of the Center for Aging Research.

CENTER FOR RESEARCH IN CHILD HEALTH

The Center for Research in Child Health (CRCH), functionally and organizationally located in the Division of General Medical Sciences, constitutes the focal point for information services in a broad area of child research. Liaison is maintained with all Institutes and Divisions at NIH having interests in this field, and with programs of the Bureau of State Services, the Children's Bureau and with non-federal agencies and organizations concerned with the health problems of children. The Center reviews research and training supported by NIH grants in making qualitative and quantitative determinations of ongoing research efforts.

During Calendar Year 1962 plans for the incorporation of the CRCH into a proposed National Institute of Child Health and Human Development resulted

in Congressional and Presidential authorization for the new Institute.

Pending formal establishment of the new Institute in early 1963, which will provide for absorption of the Center's staff and activities, the CRCH staff has undertaken the task of developing detailed plans to assimilate the Center's program into an Institute program of greatly expanded scope and function.

RESEARCH TRAINING BRANCH

The Research Training Branch of the Division, through its graduate and undergraduate training grant programs, assists qualified institutions to provide advanced training in the basic medical and health-related sciences in order to increase the numbers of high caliber investigators for research and academic careers. Through its fellowships programs the Branch supports the further training of competent scholars, thereby increasing the supply of qualified investigators, and provides increased numbers of stable career opportunities for scientists of superior potential and capability in the basic biomedical sciences.

During the Calendar Year 1962, the Research Training Branch experienced major organizational changes. Dr. Frederick L. Stone, Chief of the Branch, became Chief of the newly organized Division of Research Facilities and Resources on July 15. The vacancy created was not filled until the appointment of Dr. Harvey I. Scudder on September 17. The following executive secretaries also left the Branch to join Dr. Stone in the new Division:

Dr. J. H. U. Brown, Executive Secretary for Biomedical Engineering and Physiology;

Dr. Herbert B. Pahl, Executive Secretary for Biochemistry, Biophysical Sciences, and Nutrition; and

Dr. Raymond W. Cunningham, Executive Secretary for Pharmacology and Anesthesiology.

Other departures from the Branch included the following:

Miss Emmarie Hemphill, Executive Secretary for Epidemiology and Biometry, left the Public Health Service in January;

Dr. F. Ellis Kelsey, Executive Secretary for the Special Grant Programs, was detailed to the Office of the Surgeon General, PHS, in June; and

Mrs. Dorothy W. Conrad, Executive Secretary of the Research Fellowships Specialty Board and of the Nurse Research Fellowship Board, transferred to the Division of Research Grants as an Executive Secretary in the Career Development Review Branch in November.

On December 9, Dr. Charles A. Miller, formerly a Research Program Specialist in the Research Grants Branch of the Division, was appointed Executive Secretary for Biochemistry, Biophysical Sciences, and Nutrition.

As of the end of Calendar Year 1962, there were 49 persons in the Research Training Branch; 28 in Training and 21 in Fellowships. This compares with a total of 45 persons in Calendar Year 1961.

Research Training Programs.

During Calendar Year 1962, the availability of $28.9 million permitted the support of 598 programs in training sites of high priority as recommended by the National Advisory Health Council and other expert consultant groups. This compares with a total of 463 programs for the support of training in Calendar Year 1961, at a level of $26.1 million.

Research training programs supported during Calendar Year 1962 may be divided into three main subdivisions: the Medical Student Research Training Program, the Experimental Research Training Program, and the Graduate Research Training Programs.

Medical Student Research Training Program.

This program is designed to provide screening and research orientation for medical students by making available meaningful research training during summer, free quarter periods and drop-out years. There were 16 active grants during 1962, at a level of $896,961. This particular program serves the basic need for early selection of promising students for research in the basic biological and physical sciences, and encourages the inclusion of new natural science disciplines, interests, and competencies in the medical research training environment.

Experimental Research Training Program.

This program supports a limited number of projects for experimental research training at the undergraduate level in the sciences basic to medicine in carefully selected liberal arts colleges, geographically distributed and of representative types. Nine such projects were supported in 1962 at a level of $721,695.

Graduate Research Training Programs.

These programs support areas of recognized importance to basic biological research and research training. The disciplines receiving support during Calendar Year 1962 included Anatomical Sciences, Anesthesiology, Behavioral Sciences, Biochemistry, Biomedical Engineering, Biometry, Biophysical Sciences, Developmental Sciences, Environmental Health Sciences, Epidemiology, Genetics, Microbiology, Nursing Research, Nutritional Sciences, Pathology, Pharmacology, and Physiology.

A new program, the Medical Scientist Training Program, is now under development and is aimed primarily at the provision of a graduate level of training in the basic and clinical sciences to help prepare carefully selected students for research and academic careers in medicine. This program may well look toward the Medical Student Research Training Program as a source of selection and

indoctrination for its candidates. Only those medical schools associated with sufficiently strong graduate school departments would be qualified to enter this program.

Of the older training programs in the Division, the greatest growth in numbers of projects in Calendar Year 1962 over 1961 was in the following disciplines: Pathology by 13 new programs; Developmental Sciences by 11 new programs; Microbiology by 10 new programs; and Physiology by 10 new programs.

The Pathology Research Training Program is the largest in the Division, with 74 active grants in 1962, totaling almost $3.5 million. Of the new grants awarded, two were for training in veterinary pathology, making a total of 11 in this category. The Pathology Training Committee is greatly interested in stimulating research training in veterinary pathology; in late 1961 it sponsored a Conference in Veterinary and Comparative Pathology at Portsmouth, New Hampshire. Also in 1962, a pathology training grant was awarded to a private hospital, not directly affiliated with a medical school; one of very few such awards.

The Developmental Sciences Research Training Program in 1962 had 28 active grants for a total of $1.5 million. The grants awarded in 1962 follow the pattern of some of the previously initiated grants. Three of the new awards are in departments of obstetrics and gynecology where two or more staff members are engaged in basic biomedical or physiological research as related to developmental problems, so that the research training is centered within the department. Others depend to varying degrees on basic science departments for research training. Another, in basic biology, concentrates on training in the somewhat restricted area of gamete physiology and fertilization.

General microbiological research training is being supported in most of the high caliber medical school and graduate school departments in the Nation. Expansion on a highly selective basis will be initiated, especially in schools of veterinary medicine, and in those institutions where students, terminating at the M.S. level, are the source of recruits for Ph. D. programs in other institutions. During Calendar Year 1962, the Division supported 53 research training projects in this discipline at a level of $2.3 million.

An increase of 10 new grants in the Physiology Research Training Program in Calendar Year 1962 brought the total active grants in that discipline to 63, for a total of $2,401,136. A notable development in the new training projects was the emphasis upon higher standards in mathematics and the physical sciences. There appears to be a tendency for the fields of physiology, biomedical engineering, and biophysics to converge in terms of a common need for more rigorous science. An increasing emphasis is also being placed on comparative and cellular physiology in graduate schools, rather than on routine physiology at the medical school level.

In the Biophysical Sciences, there were nine new programs in 1962, making a total of 33 active projects, totaling $2,029,893, with scientific emphasis ranging from radiobiology and physical biology to biophysical chemistry and molecular biology.

Development of a strong program in Biomedical Engineering research training has proceeded slowly during 1962 in spite of energetic staff efforts. The requirements in this highly interdisciplinary area are extremely rigorous and a resolution of precisely what is to be achieved by program has not been effected. Extensive remedial and, later on, conjoint education is required, probably necessitating specially designed course work, at both the doctoral and postdoctoral levels for both medical and engineering candidates. In Calendar Year 1962, there were four active projects, totaling $189,545, all at the doctoral level confined to education of engineers practically exclusively. These projects propose to establish engineering scientists on a par with life science Ph. D.'s and M. D.'s working in biomedical research.

Of the 67 active training programs for research in Biochemistry in Calendar Year 1962, at a level of $3.5 million, there were seven new programs, totaling $290,574. The Biochemistry Training Committee, in addition to meeting its responsibilities for the scientific review of applications for graduate research training in fundamental biochemistry, maintained close liaison with the Committee on Educational Affairs of the American Society of Biological Chemists. In cooperation with this organization, the Training Committee held joint meetings and discussed plans for activities designed to acquaint scientists and potential graduate students with career opportunities in biochemistry. A tangible result of this joint interest was the preparation and widespread distribution to individuals and schools of an attractive brochure entitled "Careers in Biochemistry."

The Advisory Committee on Epidemiology and Biometry, in recognition of a wide variety of existing resources and a pronounced need for trained people, is looking to the initiation of applications for research training in the area of biomedical computer research. The objectives of the computer research training program would be to (1) train biomedical scientists in the use of computers and computer methodologies, including training in mathematics and biostatistics when necessary; (2) increase the number of specialists with concentration on preparation of teachers, and research scientists; (3) train biometricians with computer knowledge and skills to provide advisory services for biologists and medical research workers; and (4) provide for additional training in computer utilization for established scientists to keep in contact with new developments.

During Calendar Year 1962, there were 53 active programs in the combined disciplines of Biometry and Epidemiology, at a level of $3.1 million, including a training project in epidemiology at the University of Pennsylvania School of Veterinary Medicine; the first such program in an institution of this kind. Its purpose is to provide educational opportunities for veterinary graduate students in the basic principles of epidemiology and biostatistics leading to the Master or Doctor of Science degree.

The Pharmacology Research Training Program including pharmaceutical chemistry had 50 active grants in 1962, totaling $2,282,725. In response to the increased national concern over chemical artifacts in the environment (pollution by industrial wastes, insecticides, fungicides, herbicides, plant and animal growth factors, and various food additives) renewed emphasis has

has been placed on toxicology as a new aspect in this training program. Toxicology includes the complete study of the detection, absorption, assimilation, detoxification, pathology, and control of chemicals entering living systems from the environment.

Though the Anesthesiology Research Training Program, which functions under the Pharmacology Training Committee, had but 10 active grants in 1962, at a level of $290,164, active and constructive programming is underway for this area. Anesthesiology is a new basic science occupying an extremely important position in relation both to clinical pharmacology and to surgery. It is concerned with basic pharmacological research on procedures, evaluations, and pharmacodynamics of anesthetic agents.

In the Environmental Health Sciences, where there were 19 active projects during Calendar Year 1962 at a level of $763,613, an analysis of the 1962 applications and programs in comparison with previous years indicated a shift from civil-sanitary engineering to the multidisciplinary programs involving the basic sciences of biology, microbiology, environmental engineering, environmental chemistry, and biochemistry, as related to environmental health.

In Calendar Year 1962, the Division supported two nursing research programs, totaling $94,727. Currently the Division of Nursing, Bureau of State Services, in cooperation with the Research Training Branch, is exploring the need to establish a Nurse Scientist Graduate Training Committee; this may represent the beginning of a pioneering effort to establish a research training program for nurse scientists.

The Behavioral Sciences Research Training Program, which was formally established in March, has four active grants, totaling $179,358. The program is divided into five areas: (1) psychobiological sciences, which has a strong interdisciplinary aspect and is characterized by joint training in psychology and some other health-related discipline, such as anatomy, biometry, or physiology; (2) biosocial sciences, involving training in some of the basic subdisciplines with which sociologists are identified; (3) contributing programs, which involve ancillary training in certain advanced technologies applicable to research in the behavioral sciences, such as computer programming and electronic display, recording, and data analysis systems; (4) advanced multidisciplinary programs, which enhance the possibilities for developing new specializations by fostering the cross-fertilization of concepts and techniques between behavioral and non-behavioral sciences; and (5) special non-categorical programs.

No specific program changes where initiated in the Anatomical Sciences and Genetics research training areas during 1962. The Anatomical Sciences Research Training Program had 43 active grants, totaling $1.8 million, four of which were initiated during Calendar Year 1962. In the Genetics Research Training Program there were 35 active grants, three of them initiated in 1962, for a total of $1.9 million.

Research Fellowships and Career Awards

During Calendar Year 1962, the Division supported 1,384 fellows for a total of $6,906,912 through its Fellowships Programs. This support compares with a total of 995 fellows in 1961 at a level of $4,166,000. In the Research Career Award Program, the Division supported 30 Research Career Awardees, representing 15 states, at a level of $621,448, and at the Research Career Development Award level, there were 307 awardees, representing 33 states and the District of Columbia, for a total of $4,582,932, during Calendar Year 1962. This compares with 322 awardees in Calendar Year 1961 for a total of $4,881,097. The latter figures included the senior fellowships which merged into the Research Career Award Program in July 1961.

Funds are awarded for predoctoral, postdoctoral, and special fellowships, and grants are made for research career awards and research career development awards. The following table summarizes the fellowships and awards for Calendar Years 1961 and 1962:

Fellowships and Career Awards

Awards	Calendar Year 1961 Number	Calendar Year 1961 Amount	Calendar Year 1962 Number	Calendar Year 1962 Amount
Predoctoral Fellowships[1]	751	$ 2,529,440	1,010	$ 4,291,280
Postdoctoral Fellowships	188	1,159,078	315	2,090,444
Special Fellowships	56	477,482	59	525,188
Part-time Fellowships)[2]	572	370,656	24	15,552[3]
Postsophomore ")[2]	95	393,953	--	--
Senior Fellowships[4]	221	4,957,773[5]	--	--
Research Career Development Awards	99	1,833,771[5]	307	4,582,932
Corollary Research Grants	--	--	144	775,131
Research Career Awards	2	34,701	30	621,448
Scientific Evaluation and Planning	--	--	1	20,000
Foreign Fellowships	98	716,377[6]	--	--
Total Fellowships	2,082	$12,473,231	1,890	$12,921,975

1/ Includes fellowships in Nursing - 49, $220,042 during 1961; 60, $276,851 in 1962.

2/ As of July 1, 1961 these fellowships were absorbed by the General Research Support Program, except for Nursing Part-time.

3/ Nursing P-T program terminated on June 30, 1962.

4/ Senior Fellowships merged into the Research Career Award program in July 1961.

5/ Includes $1,925,148 from DGMS research grant funds for support of the research allowance in 1961, and $20,000 for Scientific Evaluation and Planning.

6/ This program was transferred to the Office of International Research, OD, on June 30, 1961.

In the Predoctoral Fellowship Program, which supports the further training of qualified scholars for research and academic careers in the basic biomedical and behavioral sciences, particular emphasis in 1962 was on the program areas which included biomedical engineering, biomathematics, the anatomical and physiological sciences. In July 1962, the fellowship allowance was increased to $2,500 per fellow for tuition, supplies, and travel to scientific meetings in lieu of the former tuition, fees, and supply grant. With the exception of those fellows supported by the National Institute of Mental Health and the National Institute of Dental Research, the Division has the responsibility for the support of all NIH predoctoral fellows.

The Postdoctoral Fellowships are awarded to selected, promising holders of Ph. D., D. Sc., D.D.S., M.D., as well as Doctor of Osteopathy and Doctor of Public Health degrees, who are interested in undertaking advanced research training in the basic biomedical sciences and in certain special areas of recognized importance not supported by the categorical Institutes. In 1962, particular emphasis was given to the biophysical, developmental and behavioral sciences, and to the shortage areas of anesthesiology, medical genetics, biomedical engineering, biomathematics, physiology, molecular biology, and experimental pathology.

The Special Fellowships support competent investigators contemplating additional training in the newly developed areas, such as biomedical engineering, biophysical sciences, chemical genetics, molecular biology, radiation biology, and radio-chemistry, as well as in the traditional basic biomedical and health-related sciences. This inherently flexible program provides an extremely high return on the investment made, as awards are usually made to relatively mature scientists who have completed at least three years of postdoctoral training or experience and who require further specialized training or knowledge of new techniques in order to increase their research productivity and broaden their fields of scientific competence.

The Research Career Award Program provides support in a wide variety of health-related scientific disciplines, as well as certain clinical research areas which cannot be readily identified with the interests of the categorical Institutes. The disciplines supported include anatomy, behavioral sciences, biochemistry, biomedical engineering, biometry, biophysical sciences, developmental biology, endocrinology, epidemiology, genetics, microbiology, nutrition, pathology, pharmacology and anesthesiology, and physiology. The program is designed to stabilize the income of awardees who have previously been supported from relatively unstable funds, and also to permit awardees to devote a greater proportion of their efforts to research activities. By thus increasing the number of stable full-time positions available to qualified institutions, significant support to present and future health-related research is being provided.

Research Career Awards provide support for established independent investigators of nationally recognized competence for the duration of their productive careers. Research Career Development Awards provide support for investigators with demonstrated research potential or capability who have not yet reached the stage in their scientific careers to qualify for Research Career Awards.

These awards are made for an initial period of five years but may be renewed upon adequate justification to provide a total period of support of up to 10 years.

During the Calendar Year 1962, there were 89 new awards. Of these, 25 were at the Research Career Award level and 64 were at the Research Career Development Award level. Inasmuch as excellence of research potential and achievement is the major criterion for selection of awardees, it is significant to note that of the 20 resignations from the program during 1962, seven have transferred elsewhere to accept full professorships, and, of these, four have been selected for departmental chairmanships.

The growth in the appropriations for the Research Training Branch over the past three years is indicated in the following table:

	FY 1961	FY 1962	FY 1963
Training Grants	$27,000,000	$31,000,000	$35,442,000*
Fellowships and Career Awards	10,100,000	11,290,000	14,480,000
Total	$37,100,000	$42,290,000	$49,922,000

*Includes $1.2 million for Foreign Fellowships, Office of International Research, OD.

NATIONAL ADVISORY HEALTH COUNCIL

During the year three members were appointed to the National Advisory Health Council. These were: Dr. Robert A. Aldrich, Dr. Stafford L. Warren, and *Dr. James E. Perkins. They replaced Mr. Herbert M. Bosch, who passed away in September, and Dr. H. Stanley Bennett and Dr. Sidney Farber, whose terms expired. Other members of the Council are: Dr. L. V. Berkner, Dr. Michael E. DeBakey, Dr. Edward W. Dempsey, Dr. James W. Dixon, Mr. Russell R. Larmon, Dr. I. S. Ravdin, Dr. Francis O. Schmitt, and Dr. Lewis Thomas. Ex Officio Members are: Dr. Marc James Musser and Capt. John R. Seal, MC, USN.

*Appointed February, 1963

DIVISION OF RESEARCH FACILITIES AND RESOURCES

Annual Report of Activities

For Calendar Year 1962

Summary Statement

Although this Division (DRFR) did not come into being until July 15, 1962, hence technically can report on only six months of Division activity during the past year, its five principal programs already were meeting vital health-related research needs. Briefly, here are the five:

. Oldest is the program providing for Health Research Facilities construction. Its origin was in Congressional action (PL 835) which added Title VII to the Public Health Service Act in Fiscal Year 1957. After being renewed three times -- to support critically needed health related research construction throughout the Nation -- Title VII awards authorization was increased in 1962 from $30 million to $50 million; this amount to be matched on at least a 50-50 basis by funds from private and other public sources. The total, even though $20 million more than had been provided the year before, was substantially over-subscribed by the time the appropriation was passed. This situation, after existing for six years, seems well established as a trend that can be expected to continue.

. Second oldest program is that of the General Clinical Research Centers. First applications were received in 1959 in the Division of General Medical Sciences (DGMS), following widespread recognition of the need to improve and expand the national level of clinical research in human diseases and to obtain new knowledge concerning inherent human body metabolism. There are now 60 centers operating throughout the Nation and others are forming. Early published results from studies already undertaken in these centers are now beginning to appear.

. The Animal Resources Program began in Fiscal Year 1961 with four Primate Centers under sponsorship of the National Heart Institute. These, and three others approved since, were originally established to aid research in cardiology. Their responsibility now is to provide facilities for a broad scope of scientific disciplines using primates in research. In DRFR the program will be expanded still further to include a national plan for providing all kinds of animals as needed to cover all areas of specialized medical research. There is no intention, however, to compete with services already provided by established biological supply houses.

. Also under way during 1961, was a program of Special Research Resources providing modern computers and the expert personnel to operate them, in a limited number of areas where large programs of

health-related research were in force. By December 31, 1961, grants had been awarded for five Computer Resources. By the end of 1962, 22 awards had been made, including one for a Biomedical Engineering Resource and five supplemental grants to the original five Computer Resources. Other types of Special Resources are in various stages of development.

. The General Research Support Grants program also originated in DGMS in 1961. Its formation was in answer to a long-acknowledged need for strengthening institutional research initiative and for supporting excellence in the total health-related research and research training programs at schools of medicine, dentistry, osteopathy and public health. Such awards are given on a formula basis and only to those institutions that are heavily engaged in health-related research. Before the close of 1962, plans were well along to include schools of veterinary medicine, pharmacy, nursing, and separate research institutions, laboratories, centers, and other nonprofit research organizations also engaged in health sciences research.

The Division Mission

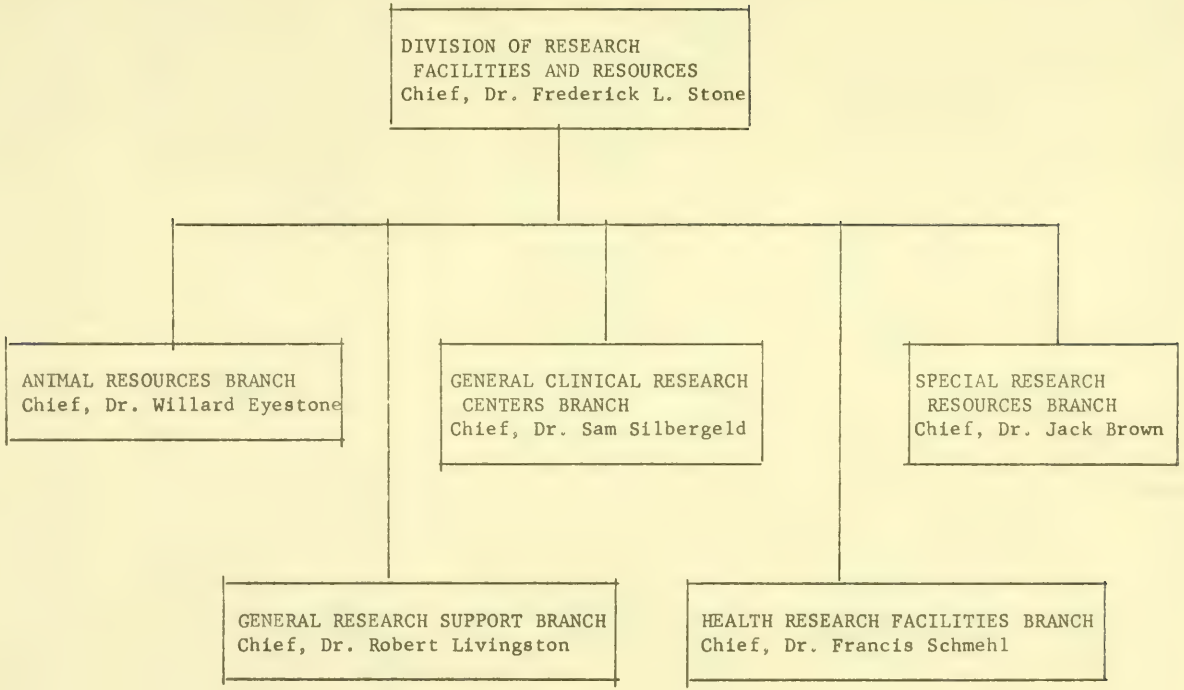
Responsibility for these five active programs was assigned to Branches within the NIH Division of Research Facilities and Resources as indicated on the organization chart. The unifying thought which knits all five together, is an overall Division objective which seeks to provide for the broad health-related research needs of institutions or groups of institutions. In this way sustained coordinated support is provided to key institutions and programs, giving their directors greater freedom in the exploration of all approaches to new medical knowledge regardless of category or discipline. Such support also gives them the capability to do pioneering work in established as well as in emergent fields of research.

Thus it is possible for a medical school or other institution already heavily engaged in health-related research, to plan for construction of a new research wing, expand its research staff, obtain service from a computer resource, increase its access to needed laboratory animals, establish a general clinical research center, and obtain an award for health-related general research support--all in a coordinated fashion--by presenting its plans to a single NIH Division. Thus all of its needs can be considered as a "package" and total aid matched with institutional progress and intellectual capacity.

Program Planning and Analysis

In the Office of the Chief, DRFR, program analysis is continuous, not only to define program objectives, to aid in the establishment of priorities, and to analyze opportunities, but to measure total achievement and plan subsequent courses of action. Frequent feedback is sent to and received from the office of the Director of NIH relating to regional and national program needs and aims. One might characterize such effort as a "commitment to excellence", for as long as institutional demands are greater than available Federal funds, in the struggle to push back the frontiers

ORGANIZATION CHART



of ignorance only those institutions deemed most capable of making a significant attack upon major health problems, can be successful applicants.

Budget

The following table summarizes funds that were available to each Division program during Fiscal Year 1963:

General Clinical Research Centers	$ 33,500,000
General Research Support	30,000,000
Health Research Facilities	50,000,000
Animal Resources (including Primates)	5,120,000
Special Research Resources	6,000,000
Applications Review and Approval	839,000
Division Administration	242,000
Total	$125,701,000

Personnel

At the end of calendar year 1962, there were 77 persons assigned to DRFR, as follows:

Office of the Chief	18
Animal Resources Branch	5
General Clinical Research Centers Branch	13
General Research Support Branch	8
Health Research Facilities Branch	29
Special Research Resources Branch	4
Total	77

Health Research Facilities Branch

Under Title VII of the Public Health Service Act, this Branch provides up to one-half of the costs for construction of buildings or portions of buildings devoted to research and related activities in the health sciences. In addition, the amount allowed may provide for up to half the cost of new equipment. In this way the program presents a powerful stimulus for institutions engaged in research to construct needed new facilities especially designed for modern biomedical research and to seek other funds to match those granted by the Federal Government. Their success in this respect is attested by the fact that over a seven-year period, $230 million appropriated for construction stimulated an investment in new and remodeled health-related research laboratories in buildings costing approximately $1 billion.

As of December 31, 1961, almost all of $180 million that up to then had been made available for matching, had been earmarked through 872 construction awards. Yet there was a growing backlog of scientifically accredited applications already approved by the Health Research Facilities Council, for which there were insufficient funds for payment. At the end of 1962,

167 new awards totaling about $50 million had been made, raising the grand total to 1039 awards amounting to $230 million. By this time, the backlog of projects approved by the Council for which there were no funds available, had reached 165, calling for $53.4 million additional. Over and above the applications already submitted, institutions whose plans are at a stage where they can give estimates of construction costs have written the Branch stating they intend to submit requests for around $30 million over the next few months. Many others are eligible and intend to apply soon, but at this time they are not able to estimate costs or provide a construction date.

It appears likely there will be many disappointed applicants in 1963. Program emphasis must focus now on aiding such broad institutional developments in health-related research as general clinical research facilities, and such regional or national facilities as animal centers, laboratories for research in mental health and mental retardation and computer centers or other special research resource laboratories.

General Clinical Research Centers Branch

Following recommendations by Congress in connection with the Fiscal 1960 Appropriations Act, the Public Health Service's General Clinical Research Centers program was started in the fall of 1959 as a responsibility of the NIH Division of General Medical Sciences. Such Centers support scientific investigators who share in a multidisciplinary, broad, integrated attack on a variety of medical problems. General Clinical Research Centers provide a stable organizational framework, an atmosphere of common purpose linking research, teaching and healing; and an intellectual environment for research of high quality. Since the initial success of this program, additional funds have been made available for categorical clinical centers administered by the NIH categorical institutes.

As of December 31, 1961, there were 32 General Clinical Research Centers in 31 institutions scattered around the country, providing 472 beds for research patients. During the past year, grants were made for 28 additional centers making a total of 60, operated by 53 institutions and capable of handling 787 research patients. Thirty-six centers with 535 beds were admitting patients at years's end. The balance are in various stages of renovation and activation. Patients admitted to these centers are volunteers. None is accepted without an understanding of what tests and treatment will be involved, how long the patient will be asked to participate, and what inconveniences or discomforts may be entailed. At no time will a patient's chances for good or improved health be jeopardized for the sake of an experiment.

The term "General" as applied to these Clinical Centers allows for variety in the types of studies prevailing. Forty-eight are adult or mixed adult-children centers; eight are for children only, one is solely for the study of premature infants and one, (at Albert Einstein College of Medicine in New York City) is a center for acute problems, studying schock, trauma, burns, sepsis, and pre- and postoperative patients. These differences

directly affect not only the nature of each facility but also the equipment needed.

In size of the centers ranges from 6 to 31 permanent beds, 0 to 7 core laboratories, and from about 2,000 gross square feet for the smallest, to 15,000 for the largest.

Most of the General Clinical Research Centers projects are still in progress, but some results already published, attest to the long-term value of the work being done.

Some idea of the research accomplishments to be expected can be gained from the following samples that have been selected from a long list of reported results:

. Muscular dystrophy has been linked to disturbances in metabolism by high-energy phosphates. Special compounds of nucleic acid may be of therapeutic value.

. Use of a transistorized "pacemaker" for stimulating the heart with radio waves has proven to be practical on seven patients with heart block. (Using the same method to study heart output at varying radio-controlled heart rates, allows determination of the optimal heart rate for each patient.)

. Certain lung cancers have been found to secrete a polypeptide which stimulates production of large quantities of adrenal cordical steroids leading to severe Cushing's syndrome (a condition characterized by obesity, muscle wasting, skin atrophy, salt and water retention, etc.)

. Use of the artificial kidney has proven its ability not only to save lives but to maintain the health of selected patients for as long as two years.

. A method of determining the life span of human blood platelets was developed and applied to studies of blood banking methods and diseases associated with abnormal bleeding.

. The first instance of genetic inborn error involving ability to metabolize short-chain fatty acids has been uncovered.

. It has been demonstrated that the anemia and hemolytic tendency of most patients with paroxysmal nocturnal hemoglobinuria (the periodic nightly appearance of red blood cells in the urine) can be corrected with iron and anabolic stroids.

Animal Resources Branch

The Regional Primate Research Centers Program, formerly a responsibility of the National Heart Institute (NHI), was transferred to DRFR in July 1962 and forms the nucleus of the Division's Animal Resources Branch program. During the first two years under NHI, funds made available to advance research in cardiology allowed grants for the establishment of four primate centers. One went to the Medical Research Foundation of Beaverton, Oregon, another to the University of Wisconsin for a center at Madison, a third to the University of Washington at Seattle, and the fourth to Emory University for a center in Atlanta.

During Fiscal 1962, Congress appropriated $9.5 million for primate research centers and three new awards were made, one each to Harvard University, Tulane University, and the University of California. Each award provides two grants, one for total construction costs including land, and one for operating costs for a period of 7 years. Total amount awarded for construction to December 31, 1962 was $13,740,056. The terms of the awards require each institution to serve as a "host" establishment, not only for fiscal management, but to provide an academic environment of high standard for resident and visiting scientists.

Although each center has its own program, six are regional centers committed to providing facilities for a broad scope of disciplines using primates in research. The seventh, at Davis, California, will be a National Primate Conditioning Center, committed to investigations on the primate itself; including capture and transportation, maintenance under laboratory conditions, and breeding and rearing in captivity. This center will also be a source of supply for animals with unique characteristics unobtainable from any other source.

Currently, the Animal Resources Branch has three main objectives:

(1) to support the primate centers program,
(2) to develop a national effort to provide the types, quantities and quality of any species of animals needed for a variety of areas of specialized biomedical research,
(3) to determine optimum conditions for laboratory animal care, including their safety and medical treatment.

As of December 31, 1962, the following report can be rendered on each of the centers thus far approved:

Oregon Regional Primate Research Center

This unique new facility, which includes out-door colony buildings, is on a large tract of land in Beaverton, about 10 miles west of downtown Portland. University of Oregon sets the scientific standards by which this center operates. Investigators at the facility currently feature studies on vital processes involved in heredity and in the origin, specialization, and functional mechanism of primate cellular and organ

systems.

University of Wisconsin Regional Primate Research Center

Construction of this facility began in December 1962 on a site in the campus extension area adjacent to an existing primate laboratory. An extensive breeding program will be undertaken here to provide a constant supply of young rhesus monkeys for scientific studies. Such studies will include biochemical factors associated with mental retardation, postnatal development of the primate brain, hormonal factors in reproductive processes, and variables influencing the development of normal and abnormal behavior. One area will be for the housing of animals where life-time studies of the rhesus monkey can be continued from birth to death--a life span that can range up to 25 years.

Regional Primate Research Center of the University of Washington

Grants have been awarded, construction plans are in the final drafting stage, and construction of a regional primate research center is expected to begin on the University of Washington campus at Seattle early in 1963. In addition to providing primates for medical, biological and psychological researches by university faculty members, this center will also emphasize the training of visiting scientists in primate research techniques and primate care.

Emory University's Yerkes Regional Primate Research Center

Multidisciplinary studies using primarily the greater apes are planned for the Emory center, for which grants for construction and operation have been awarded. The building of a new facility is scheduled to begin during the summer of 1963. An existing colony of chimpanzees and other primates currently located at Orange Park, Florida, will be transferred to Atlanta when the new facility is ready.

New England Regional Primate Research Center

Grants were awarded in 1962 to the Harvard Medical School acting in behalf of several New England universities and medical institutions, to construct and operate a regional primate research center on a tract of land in Marlboro and Southboro, Massachusetts. Construction is to begin late in 1963.

Delta Regional Primate Research Center

Grants were awarded in 1962 to Tulane University for construction and operation of a primate center near Covington, Louisiana, about 26 miles from New Orleans. Research emphasis here will be on infectious diseases, genetic and developmental disorders, chronic and degenerative diseases, radiation, and behavioral studies. Construction is to begin during the summer of 1963.

National Primate Conditioning Center

Grants were made to the University of California in 1962 for construction and operation of a national facility for conditioning primates. Building is scheduled to begin late in 1963.

This center will serve as a national resource for the study of a wide variety of primates with emphasis on their capture, transportation, and methods of keeping them in good condition. Breeding facilities will be expected to provide data on large-scale controlled production, and allow for the breeding of animals possessing genetic and other special biological characteristics essential in biomedical research.

Special Research Resources Branch

This Branch traces its origin to a Committee of Consultants on Medical Research to the Subcommittee on the Departments of Labor and Health, Education and Welfare of the Senate Committee on Appropriations, whose members recommended[1/] the use of modern computers and other types of specialized equipment wherever large programs of health-related research were underway. They also recommended the support of communication science research, specifically, for "a greatly increased research effort on methods of data processing, literature analysis, and information retrieval in both the intramural and extramural programs of the NIH."

This last mission was added to the programs of this Branch in November 1962 and there has been time for little more than the preliminaries to program planning.

Work toward the development of computer research resource centers began in Fiscal Year 1962 when $5 million was made available for this purpose in the Division of General Medical Sciences. With an additional $6 million available for Fiscal 1963, and after a broadening of Branch planning, October 1 saw 18 programs (now all activated) transferred from DGMS to DRFR. Seventeen were for computer centers and one was for biomedical engineering.

One of the established centers has already demonstrated the effectiveness of the computer not only in the research projects of the medical center of the university in which it is located but also in those of several other institutions which, through a cooperative arrangement with the center, have used the computer in their own research.

Among those institutions and agencies are State mental hospitals, Veterans' Administration hospitals, public health departments, a number of medical schools and voluntary health agencies. Studies for which the

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1/ Report issued in 1960.

center has been used include the monitoring of fetal heart sounds, factor analyses of surgical risks, air pollution, blood pressure and tranquilizers, the analysis of electroencephalographic records, correlation of ketosteroids to obesity, and the relation of therapy methods to types of cancer.

At another location there has been great interest this past year, in neuroelectric activity and its relationship to computer design. The recently developed Laboratory Instrument Computer (LINC) was clearly a response to the need for a machine capable of accepting analog input, converting this to digital form, evaluating and displaying the output in different ways. While this is a very modest machine, containing elements already well within the state of the art, its use in the laboratories of physicists and physiologists is expected to create a demand for a much increased capability. When this point is reached, demands may be made of the computer engineer which cannot be resolved by techniques within the present state of his art. It is quite possible therefore, that developments in memory and logic will lean heavily on the experiences of neuroelectric and neurochemical biology.

As more scientists become aware of the potential of computers for speeding research and facilitating investigation into problems once considered either too difficult or insoluble, the demand for computer centers is expected to increase rapidly. Reviewed at the November 1962 National Advisory Health Council meeting were 15 new applications; 13 for computers, 1 in biomedical engineering and 1 in the biomedical information field. Of these, 5 were approved and 1 application was deferred pending a future site visit. At years end, contract negotiations were well under way to explore the present capabilities of a special type of resource at a center to be established at the Massachusetts Institute of Technology.

Although program emphasis has thus far been preponderantly oriented toward developments in computer technology and computer usage for health-oriented research, it is expected that an increasing number of applications will feature other types of centers. These too, will be designed to aid institutions or regions totally, so that they can advance or improve their research capability and thus contribute powerfully to combined multicategorical attack on the dread diseases.

Throughout the scientific community there is a distinct trend toward large-scale projects, a greater emphasis on long-term studies, an increasing cost of complex apparatus, a necessity for higher paid, skilled, technical supporting staffs, and a steady need for increasing the funds necessary to support individual workers. All of these tend to make a special resource facility the most satisfactory method for providing research support to large programs.

General Research Support Branch

In 1959, as part of its appraisal of the impact of its support programs on grantee institutions, the National Institutes of Health undertook an intensive short-term study of 20 medical schools. All reported a rapid

expansion in research activities over the past few years. This they labeled as distinctly advantageous in that it had contributed to the advancement of scientific knowledge, enhanced the quality of education, elevated the stature of their faculties and provided new strength to schools. None voted for research retrenchment. All expressed the hope their research programs would continue to grow. Nevertheless, most schools identified a number of problems engineered by funds provided in the form of restricted gifts and grants -- particularly those from Federal agencies.

Next came the report of the President's Science Advisory Committee on "Strengthening American Science." In this the Committee asserted "institutional grants for specialized fields is another instrumentality (in addition to project grants and program grants) that should be encouraged in providing support for Government-sponsored research in non-Government installations."

Meanwhile, discussions had been going on at NIH for several years, concerning the wisdom of achieving better support balance by making base grants for research and research training, such grants to be distributed on the basis of professional evaluations of the unique capabilities and needs of the various institutions. It was decided they would not be made to finance specific projects on programs but would be for use by grantee institutions to provide strength to their medical research and research training programs in ways the institutions might judge to be most effective -- subject, of course, to the general guidelines and policies affecting all Public Health Services grants.

First awards under the new program were made in January 1962. By the end of the fiscal year a total of $20 million had been awarded to 86 medical schools, 49 dental schools, 12 schools of public health and 6 schools of osteopathy. This amounted to approximately five percent of the amounts provided for grants for research projects through the appropriations for the NIH.

For Fiscal Year 1963, $30 million was made available and the General Research Support program permits (upon the satisfaction of certain criteria) the extension of support to schools of pharmacy, nursing, and veterinary medicine; and to research institutes, centers, certain laboratories and other nonprofit organizations heavily engaged in health-related research.

General support awards are made according to formula and represent a percentage of the amount of Federal research project grants and contracts awarded to institutions, plus a somewhat larger percentage based on an institution's available research funds received from non-Federal sources. The greater weight assigned to this latter factor is intended to provide an incentive for institutions to seek out additional non-Federal funds.

That general support funds have helped institutions develop the better balanced research and research training programs originally envisioned, is attested by information obtained through visits to schools, from correspondence and other informal channels. (Formal reports have not yet been received. First reports are due for submission early in 1963.) It has been learned,

for example, that some institutions have been upgrading and strengthening science departments by adding senior research staff in research areas previously not available at that institution. As a consequence, they have been able to meet criteria for other research and research training grant funds for which they were not able to compete in the past.

One school, for example, established and staffed a new experimental endocrinology laboratory. Within the next year or so, salaries paid from the grant will be picked up on the university budget, thus releasing General Research Support Grants funds for the development of other research activities. This school also provided and staffed a new animal surgery for research, established an instrument development shop for the research support of several basic science departments, and undertook a pilot study on the breeding of animals for research. The same award also provided support for several students beginning their research training at the post-sophomore level.

Another school appointed three top-level research professors in 1962 and engaged a fourth to join the staff in 1963. Meanwhile, the research potential of several faculty members was increased by putting them on a twelve months' salary instead of the usual nine.

A third institution established three new divisions of wholly independent research activities--one for Neurophysiology, another for Molecular Biology in the Department of Biochemistry, and a third for Genetics in the Department of Microbiology. The grant also provided basic salaries for a number of professionals and paid the costs of needed new equipment.

A more complete evaluation of the General Research Support Grants Program will be possible during 1963 when formal reports will have been received. A comprehensive analysis of these can be expected to provide valuable guidelines for future operations.

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Annual Report of Program Activities
Division of Research Grants
Calendar Year 1962

Summary Statement

The Division of Research Grants coordinates and services the grants and awards programs established throughout the Public Health Service. This represents an expansion of DRG's activities during 1962 to encompass all extramural programs of the Bureau of State Services, as well as the continually growing granting activities of the National Institutes of Health. In fiscal year 1962, these PHS programs included 23,747 grants and awards, totaling $571 million.

To facilitate management of these diverse extramural endeavors and provide guidelines for future medical research and health planning, a system for integrated collection, analysis and publication of data on all grants and awards was initiated in 1962, employing the Honeywell-800 electronic computer.

Early in the year the Interbureau Advisory Committee for Extramural Programs was established as the executive committee for grants policy and administration. The Committee, headed by the Chief of the Division of Research Grants, serves as an advisory group to the Surgeon General and is responsible for developing policies and procedures relative to extramural grants, fellowship and training activities. Representatives from each of the major granting programs are committee members.

A new manual setting forth guidelines for the management of Public Health Service research and training grant funds neared completion, with a section on research grants published and distributed. The "Manual to Facilitate the Administration of Research and Training Grants" is to help business managers in recipient institutions in providing fiscal control of grants, and to document responsibilities accompanying the use of public funds. The research grants section became effective January 1, 1963, superseding all previous relevant instructions.

A program of orientation seminars at grantee institutions supplements the Manual for explanation and discussion of the changing fiscal picture in grants management. A panel of three DRG representatives visits universities and research organizations to clarify support programs, and to exchange views with local administrators, faculty members, public information officers and others concerned. The first visit under this program was in November to Western Reserve University in Cleveland, Ohio.

A second publication highlighting the year was the first edition of The Research Grants Index, a scientific subject-matter index to current research supported by PHS grants programs. Designed to aid scientist to scientist communication, the 681-page Index contains approximately 8,000 subject headings covering work in progress on over 14,000 projects. An up-to-date volume of the Index will be published annually.

Major personnel changes during the year were the appointment of two assistant chiefs of the Division. Clarence A. Lowe was promoted from the post of Chief of the Grants Management Branch, and Eugene A. Confrey came to DRG from the Office of Research Grants, Bureau of State Services. New Chief of the Grants Management Branch is Sidney B. Cohen, previously Assistant Chief and Acting Chief of the Branch.

The Grants Associates Program, created to recruit and train professional staff in PHS grants administration, was underway and making progress with eight grants associates in training. A year-long schedule of assignments gives the associate an opportunity to rotate through different institutes and divisions to obtain experience in the many-faceted grants operation.

Four new study sections were created in 1962, bringing the total to 46. In addition to initial review of all research grant applications, the study sections continued to stimulate and organize conferences, symposia and other meetings for exchanging information on specific health and medical problems.

The DRG grants and awards exhibit was displayed at many scientific meetings across the nation and has been a valuable and efficient medium for informing scientists about the broad array of support available from the separate institutes and divisions of PHS.

OFFICE OF THE CHIEF

Information Office

The Information Office of the Division of Research Grants plans and executes both day-to-day and special information activities on the policies, programs, and achievements of DRG. Information on the technical and administrative aspects of the NIH extramural programs for research, training and construction, is also planned and developed, employing a variety of media.

With the increasing participation of other PHS divisions and institutes in grants and awards programs, the DRG Information Office is a focus for answering a wide array of requests relating to extramural programs from NIH, the Bureau of State Services, the Public Inquiries Branch of the Office of the Surgeon General, and other governmental and non-governmental agencies and units.

Responsibilities of the Information Office therefore include preparation for the Congress of annual and special reports on the program of the DRG; writing releases for publication in the general and specialized press; preparing speeches and other materials requested by Division, NIH, PHS, and Department officials; providing to the working press such information and assistance as needed; preparing weekly reports on program developments for the Surgeon General; handling telephone or mail inquiries from the public; providing editorial assistance as required; participating in the clearance of manuscripts; and other related assignments.

During 1962, the exhibits program of the Information Office continued to grow, with two exhibits being displayed throughout the United States and a third in preparation. The use of audiovisual aids for effective technical and scientific communication has also been extended through preparation of slides, charts and posters. A film library is being developed with revision of the film "How A Research Grant is Made" and preparation of film strips in progress, and a selection of transparent slides on hand.

The DRG Library, located in the Information Office, continued in 1962 to serve as a repository for scientific journals and other published materials pertinent to planning and administering research grant programs. The Office also houses the current Grantee Institution File, a collection of facts on research developments, personnel changes, press releases, etc. in institutions receiving PHS extramural support, to further maintain its ability for supplying useful information on grant and award activities.

The Information Office during 1962 spearheaded a new program of information seminars, involving visits by DRG executives to grantee institutions, for exchange of views on policies and procedures on grants and awards, with special attention given to clarification and discussions of new DRG and PHS programs.

Office of Research Accomplishments

This office's function is (1) to promote accelerated communication between scientists in their respective fields; (2) prepare analytical studies of ongoing research and of accomplishments in different research areas; (3) to survey "gap" areas where further research is seriously needed; (4) to make a continuing longitudinal study of "research potential," and (5) to prepare background material for addresses at scientific meetings and for papers to be published in scientific journals.

Examples of these activities are the promotional "100 Problems" program that has resulted so far in the publication "100 Problems in Environmental Health" and "Some Problems in Oral Health"; the "Forward-Oriented Reviews" program leading to publication of reviews in limited areas showing what has been done and what needs to be done in the area; periodic polling of Study Section membership to identify recent research achievements of outstanding importance and to identify pressing problems that need attention (poll now in progress, results to be compiled and copies mailed to each Study Section member).

Examples of studies of ongoing research have been a survey of NIH-supported research in one of the states, research on germ-free animals, research in schools of pharmacy, research having to do with pesticides, and of all research, regardless of supporting agency, in reproduction as related to birth and population control.

The office has also promoted the creation of information exchange groups, the first of which was started on an experimental basis in the field of Oxidative Phosphorylation and Terminal Electron Transport. Scientists in the same field of medical research interest are invited to membership in these

groups for the mutual exchange of research findings prior to publication of their manuscripts in the scientific journals. This program is still in its infancy, but already shows promise of becoming an effective method for accelerating communication of research findings.

The Office of Research Accomplishments also undertakes studies which are basic to the preparation of papers for presentation of scientific gatherings, and for publication in scientific journals. It also prepares background material for replies to political requests for information on the program and its management and for the information of Advisory Councils and PHS personnel. Statistical data are also prepared in support of the material mentioned above.

Research Documentation Section

The first edition of the Research Grants Index (PHS Pub. 925) appeared in May, 1962. This volume, which will be revised annually, is a scientific subject-matter index to current research supported by the Public Health Service research grants programs. The 681-page Index contains approximately 8,000 subject headings and represents analyses of over 14,000 projects. Nearly 22,000 copies of the Index have been distributed to PHS grantees and to other scientists and scientific institutions in this country and abroad.

An important prerequisite for the preparation of the Research Grants Index was the compilation by the Research Documentation Section of the DRG of a thesaurus for use as an indexing guide. The thesaurus now contains approximately 8,000 subject headings, 1,300 "see" references, 8,000 "see also" references, and 900 "use" terms. The thesaurus is now programmed for the NIH computer (MH-800) from which the Section receives monthly updated runs for use as indexing guide manuals.

The Research Grants Index publication is presently prepared by a photographic technique; i.e., sequential camera cards from which negative film copy is prepared by a Listomatic camera. Computer programs are being prepared, however, and we anticipate that by the end of 1963, the copy preparation of the Index will be done by computer. Computer print-out is expected to reduce copy preparation time from nine to two weeks as well as to provide facilities for furnishing excerpted lists from the Master Index on demand.

In 1963, the Section also will index NIH intramural research for preparation of a companion intramural volume similar to the extramural Research Grants Index. The intramural index will include all research projects beginning with the calendar year 1962.

Patents

Two major developments have occurred in the administration of inventions resulting from PHS grant and award programs during the past year.

1. Under a change in invention reporting procedure, effective March 1, 1962, submission of an Annual Invention Statement is required on a PHS form as part of all requests for renewal of support and as part of all final progress reports. This Statement is additional to the requirement to report

formally to the Surgeon General all inventions arising from PHS support, and is intended to call the reporting obligation to the personal attention of scientists and institution officials on a regular basis.

2. A requirement to provide a statement of commitments or obligations which would be in conflict with PHS inventions and patent policy was put into effect on October 15, 1962. An insertion in all application folders sets forth this new requirement that the PHS be advised prior to the award of Government funds of any commitments or obligations made by the institution or by the professional personnel to be associated with the project, which would be in conflict with the inventions agreement in the application for PHS funds.

Until application forms are revised to provide for this information, all applications submitted for PHS funds must be accompanied by a letter stating that no previous commitments have been made or a detailed explanation if any have. The letter must be signed by the individuals who are authorized to sign the application.

Grants Associates Program

During 1962 the Grants Associates Program, inaugurated in 1961, made notable progress in preliminary efforts designed to recruit and train scientists for the extramural programs of all granting divisions of the Public Health Service.

As of November 1962, eight grants associates were in training with full schedules under the program. Basically, each trainee's own experience, previous training and interests help determine the specific pattern his training program follows.

A senior scientist at the National Institutes of Health or the Bureau of State Services is assigned to each associate as a preceptor. Throughout the one year training schedule these preceptors give individual guidance and careful supervision to their assigned associates as they are trained in particular program areas. Cooperation by these "tutors" has been excellent.

While in training, an associate rotates through different program areas to obtain experience in grants administration, manpower training resources and other categories relating to the overall grants management picture. Training assignments covered during the year may include work in several institutes, the Division of Research Grants and the Bureau of State Services.

In addition to regular program schedules, three seminars are offered to the associates. These seminars include: (1) A series of informal meetings with key staff members from various divisions and institutes of the NIH and the BSS; (2) A presentation of the organization, administration and programs of the PHS; and (3) A series on public administration presented by the American University School of Government and Public Administration.

During calendar year 1962 the Review and Referral Branches were reorganized and combined to form the Research Grants Review Branch.

The total number of study sections now active in the Division reached 46 with the establishing of four new sections in 1962. The Neurology, Medicinal Chemistry and Mental Health Study Sections were each split into two parallel groups and the Sensory Diseases Study Section was divided into the Communicative Sciences Study Section and the Visual Sciences Study Section.

A total of 10,028 research proposals were processed and reviewed. This represented an increase of more than five percent over the proposals reviewed in 1961. The cost of the study sections' review of applications was approximately $857,000 and required 6,860 man days in terms of consultant services.

Of significant interest was a plan which was developed during the year to permit the capture of pertinent data from research grant applications immediately following assignment. This data would be captured by means of automatic typewriters and prepared as input for analysis by high-speed electronic digital computers. Code symbols for the mechanized operation were also developed.

The Committee on Advanced Research made important contributions to the scientific posture of the Research Grants Review Branch. The purpose of this Committee is to find ways and means to encourage work at the frontiers of knowledge, based on theoretical innovations and requiring the development of new research methods.

The Study Sections

In addition to their responsibility for conducting the technical review and appraisal of research applications and making recommendations to the Advisory Councils, the Division's 46 study sections also develop and encourage research in neglected areas of the health, medical or related sciences.

During the past year, the study sections planned and programmed a variety of scientific conferences; sponsored the publication of proceedings of selected symposia; conducted evaluations of their individual programs and programmed in new areas; and engaged in a wide variety of other related activities.

A number of the study sections have been reorganized and redirected in order to strengthen various areas of research grant review. Some of the significant activities within the study sections during 1962 follow.

Accident Prevention Research

At its three meetings in 1962, the Accident Prevention Research Study Section reviewed 55 research grant applications and two applications for fellowships. As in previous years, the majority (63 percent) of the proposals dealt with some aspect of motor-vehicle accident prevention. Seventeen percent

of the proposals were broadly oriented and would provide information applicable to all or several classes of accident; i.e., they dealt with a specific manner of injury, such as falls, or with accidents to children. The remaining 20 percent (11 applications) proposed studies of home accidents, agricultural, aviation, industrial or sports accidents.

Research grants paid in fiscal year 1962 amounted to $1,917,419.

The expected increase in requests for extramural research support in accident prevention has not as yet materialized. Part of this failure to grow can be attributed to lack of awareness among potential researchers that grant money is available for studies of this subject. Other factors are the limited number of competent researchers in the field and the fact that accident prevention is not a discrete discipline for which training and the development of research skills is generally available as an established curriculum. Though the Study Section, which represents such diverse disciplines as traffic and industrial engineering, psychology, education, mathematics, epidemiology, medicine, and henceforth sociology, is eager to see improvement in the quality of applications, it has not addressed itself to delineating the means of attaining this goal.

At the request of the Division of Accident Prevention, Bureau of State Services, the Study Section has continued to review applications from profit-making organizations. This is being done to provide the Division guidance in arranging research contracts for scientifically sound proposals from this category of organization, no longer eligible for research grants. A drawback in these reviews has been the absence of a suitable yardstick for judging the appropriateness of the overhead requested by large corporations, which are allowed a higher percentage overhead on defense contracts than is available under Public Health Service research grants.

In coming months, the Study Section intends to become better acquainted with developments reported by investigators conducting research projects supported by accident prevention grants.

In connection with reviewing an application for added support for a current project in driving simulation, the Study Section has expressed itself as being unsympathetic to the support of extramural research for development of apparatus per se to the exclusion of use of the apparatus in a related research program or a theoretical orientation. This statement of principle should be a useful guideline in reviewing proposals.

Cardiovascular

Cardiovascular Study Section review of applications continued to increase during calendar year 1962 with 385 reviews compared to 370 in 1961. Of the total, 220 were recommended for approval and 139 disapproved.

In connection with the reviewing process, Section members made project site visits concerning 24 separate applications. During the year the number of applications recommended for approval increased slightly, probably due to a wider use of local screening procedures in many institutions, whereby poorer

applications failed to receive local approval and therefore were not submitted for review.

The pressure of a heavy regular workload made it impossible for the Section to hold general discussions concerning the adequacy of research being conducted in the specific areas in which it is concerned. However, Section members, realizing this is a pertinent function of advisory consultants, are presently making plans to incorporate time for appropriate general discussions. No ad hoc consultants were brought together for a discussion of the developments and needs in any specific area, as was done the preceding two years. This was also due to the heavy workload.

Cell Biology

The Cell Biology Study Section has reviewed approximately 390 applications during the calendar year, in the fields of cytology, cytochemistry, histology, histogenesis, histochemistry, vertebrate and invertebrate embryology, anatomy, cell growth, nucleocytoplasmic relationships, the biochemistry of nucleic acids and of enzymes, marine biology and other related fields.

In addition, the Study Section, which was largely responsible for organizing and implementing the formation of the American Society for Cell Biology, has continued to guide and lead the activities of this Society. The second annual meeting of the Society was held in November 1962, in San Francisco, with Dr. Heinz Herrmann as Program Chairman, Dr. Hewson Swift as one of the main speakers, and Dr. Rollin Hotchkiss as a member of the Council, all current members of our Study Section. Former members who were active participants in the meeting were Dr. Keith Porter, Dr. Charles B. Metz and Dr. Harry Eagle.

Communicative Sciences

During July 1962, the Communicative Sciences Study Section was established, reflecting recognition of the increased research activity in the fields of speech, hearing and communicative disorders.

Five members of the now disbanded Sensory Diseases Study Section joined the new Study Section, and twelve additional members were appointed. The Section's multi-disciplinary composition was indicated by the membership of the new panel, which includes experts from the following fields: Otolaryngology, audiology, acoustics, speech and phonetics, physiological psychology, neurophysiology, electronics, maxillofacial surgery and tissue culture.

The Study Section reviewed a total of 40 applications at its first meeting held in September 1962. Approval was given to 25, or 62.5 percent of these, 12 were disapproved and 3 deferred for further study. In connection with review of applications Study Section members visited five project sites.

For the immediate future the Communicative Sciences Study Section will concentrate on the review of research grant applications and discussions of the most adequate means for stimulating research in the neglected areas of

the communicative sciences. As of this report, the Study Section has not undertaken any special projects or activities.

Computers in Research, Advisory Committee on

Pursuant to its Interim Report of June 1961, the Advisory Committee on Computers in Research in January 1962, submitted to the Director, NIH, a report entitled "Guidelines for NIH Support of Biomedical Computing." This report was planned as a more detailed delineation of the Committee's assessment of developments in the field of biomedical computing throughout the country and their recommendations on the most beneficial ways in which NIH can encourage future progress in this field. Dr. Shannon presented his comments on the report to the Committee at their April 1962 meeting. He emphasized the urgent need to support graduate training programs aimed at alleviating the critical shortage of personnel skilled in the application of computer technology to biomedical science.

As a part of the educational function of ACCR, a conference was held at the University of California, Los Angeles, October 13 and 14, 1962, on the subject "Conceptual Bases of the Biocommunication Sciences." In four sessions the major theoretical areas involved were explored in terms of existing models and their appropriateness for the biological scientist with attention to the validity of existing abstractions, the relation of these to biological reality, and their potential for the future. A number of prominent mathematicians and biologists were invited to speak, including representatives from Germany, England and Russia. A post-conference workshop was held to review, analyze and synthesize the material that was presented at the Conference.

Dental

During calendar year 1962, the Dental Study Section reviewed 243 research grant applications of which 112 were recommended for approval, 112 for disapproval, and 19 for deferral.

The Dental Study Section continued its program of organizing conferences to encourage research in the many areas of science related to dental health. Professor Phillips and Drs. Levy, Ryge and Conner of the Dental Study Section were members of the organizing committee for the Conference on Adhesive Restorative Dental Materials held at Indiana University Medical Center, Indianapolis, Indiana, September 28 and 29, 1961. The workshop was sponsored by the Dental Study Section and its Proceedings were distributed in July of this year. Professor Phillips was editor and Dr. Ryge co-editor of the Proceedings.

The International Conference on Salivary Glands and Their Secretions sponsored by the Dental Study Section was held August 27-29, 1962 at the University of Washington in Seattle. Dr. Leo M. Sreebny acted as Conference Chairman. Dental Study Section members who participated in this Conference were Drs. Leung, Levy, Zipkin, Rovelstad and Conner. The Conference was endorsed by the National Institute of Dental Research and partially supported by a grant to the University's School of Dentistry from the United States Public Health Service. This was the first international meeting devoted solely to this subject. Dr. Zipkin, reporting on this Conference at the September

1962 meeting of the Dental Study Section, stated that the Conference was very successful and highly productive. Copies of the Proceedings will be available in the near future.

A report on arrangements for the Conference on Trigeminal Anatomy and Physiology was given by Dr. Gibilisco, Chairman of the Planning Committee. The Conference, to be supported by NIDR, will be held September 1963, in Rochester, Minnesota, and planning sessions are now in progress to organize the agenda.

At its September 1962 meeting, the Dental Study Section adopted a motion for formation of an Action Committee to make concrete suggestions for solution of problems in encouragement of dental research. The Chairman of the Study Section is Chairman of this Committee, which will prepare a report to be submitted to the Study Section for approval, and then be sent to appropriate organizations.

Endocrinology

Endocrinology Study Section programs involving the preparation and distribution of hormones and radioactively labeled steroids, experienced increasing demands for materials during 1962 and continued interest in these programs was evident.

A urinary gonadotrophin of high potency, prepared under an NIH grant by Dr. Alexander Albert of the Mayo Foundation, was packaged and is now available for world-wide distribution.

Arrangements for monthly notices to be published in endocrine journals are now under way. Materials currently available for distribution under Study Section programs will be listed. It is expected that investigators will become accustomed to referring to these journals for information regarding current status of programs, thus obviating voluminous correspondence.

Negotiations were begun between NIH and the Medical Research Council of the United Kingdom to join in a cooperative for the collection and distribution of commercially unavailable steroids. It is anticipated that through this effort rare steroids will be made readily available as standard materials, for a variety of purposes, to investigators throughout the scientific world. It was the opinion of Study Section members that it was more feasible to join with the MRC programs than to initiate a separate organization for identical purposes.

Methods of isolating growth hormone from human pituitaries, and the finding that human growth hormone is species specific, led to an increase in demands for human source material for investigative purposes. Increasing the number of human pituitary glands available to investigators became a prime interest of the Study Section and as a result of vigorous stimulation by the Endocrinology Study Section, a research grant application for the establishment of a national human pituitary collecting agency was forthcoming and is now being processed for Council review.

A Workshop on Estrogens, proposed and organized at the request of the Study Section, will be held in Seattle, Washington in early April 1963. Pres-

ent plans call for the proceedings to be published in book form.

During 1962, approximately 400 applications for grants were reviewed by the Endocrinology Study Section, with resultant recommendations forwarded to respective Councils.

Environmental Sciences and Engineering

The Environmental Sciences and Engineering Study Section reviews applications in four major areas: Air Pollution, Water Pollution, Food Sciences and Occupational Health.

During 1962 a total of 375 applications were reviewed with 50 percent of this number being recommended for approval.

Because of the increasing number of applications, the multicategorical areas and the many scientific disciplines involved in the broad field of the environmental sciences, the Section currently has twenty voting members. Consideration is now being given to the possibility of splitting the Section should the workload continue to increase.

Because of the establishment last year of the five Divisions in the BSS in areas of the environmental sciences with which the Study Section is directly involved, there can be expected an intensified program of activities to encourage training and research. As a result of the great emphasis being placed on environmental health on a national scale and the lack of trained scientists and programs to foster necessary research, the Study Section organized a Program Planning Committee during the early part of 1962 in order to be in a better position to aid the PHS in efforts to develop and strengthen the environmental sciences field.

The Committee's primary objectives, as expressed at its first meeting, are as follows:

(1) Determine means of securing top level students from basic science disciplines for graduate study and specialization.

(2) Arouse interest in university faculties to the expanding programs and needs in the environmental sciences.

(3) Attract highly trained basic scientists to research and teaching careers.

(4) Cooperate with other professional groups with similar objectives and interests, for example: the research committees of the American Sanitary Engineering Intersociety Board, Water Pollution Control Federation, American Water Works Association; other Study Sections with related interests such as Toxicology, Parasitology and Tropical Medicine Sections; the National Research Council Committee on Environmental Health; international groups such as the Pan American Health Organization; and the Bureau of State Services.

(5) Develop and plan conferences and symposia for the purpose of stimulating new concepts in research and training and dissemination of information.

(6) Study of undergraduate and graduate school curricula for training personnel and definition of the areas and disciplines that should be included and emphasized.

During 1962 the Planning Committee, consisting of seven members under the chairmanship of Dr. Hovhaness Heukelekian, met four times. The following activities have been undertaken:

(1) Three members of the Planning Committee volunteered to serve and were invited as consultants to the National Research Council and BSS in planning a training conference in the environmental sciences to be held in the spring or summer of 1963.

(2) The Planning Committee developed a Conference on Graduate Opportunities in Environmental Health (through a research grant) to be held in the spring or summer of 1963. The purpose is to exchange information on research needs and career opportunities and possible sources of scientific manpower trained to meet these needs. Representatives of 75 colleges and universities from the Northeast will be invited to participate. Topics for discussion will include interdisciplinary research such as biological effects and control of ionizing radiation exposure, conservation of air resources, waste disposal, water pollution, food protection and occupational exposure.

(3) The Committee is currently planning a research conference on agricultural chemicals and food additives in order to examine critically the techniques in assessing any direct or indirect hazards of such chemicals and to review and integrate the present status of knowledge in the controversies arising from the use of food additives, pesticides, herbicides, and insecticides. The Toxicology Study Section has been invited to participate in this effort.

(4) The Committee has been considering ways in which it might encourage the development of environmental health research in Latin America. Discussions have already been held with officials of the Pan American Health Organization and Agency for International Development and the BSS who agreed to cooperate in any effort of the Section to stimulate research in Latin American countries in food sanitation, housing, air and water pollution, radiological and occupational health. A request has been made to the Chief, DRG, for three members to make an exploratory visit in early March 1963 to three Latin American countries.

(5) The Division of Environmental Engineering and Food Protection of the BSS informed the Planning Committee that there has been considerable interest by individuals and organizations such as the American Public Works Association to hold a conference on solid waste disposal and inquired whether the Study Section would co-sponsor and plan such a

conference with the Division. Consideration was given to the fact that the problems of solid waste disposal have received insufficient attention from engineers and research personnel in the past. Yet, these problems are more acute and overwhelming than those in the liquid and air phase of waste disposal. In Los Angeles, for example, the total tonnage of solid wastes is approximately seven times that of the sewage and industrial wastes, on a dry-solids basis. Furthermore, the cost of solid waste disposal is in order of five to eight times as much as the cost of sewage collection and treatment. In contrast, there are very few research projects sponsored in the fields of solids waste disposal in relation to the scores of projects in sewage and industrial wastes. The Committee, therefore agreed to the necessity and urgency of holding a conference and under the chairmanship of Dr. Ross McKinney is now organizing a program for consideration of the Study Section. In this connection the Study Section will, in conjunction with its regular meeting in January, attend an Orientation Program on Research Needs in Solid Wastes Disposal that is being arranged by Dr. Jack McKee at the California Institute of Technology.

In addition to the Section's current planning activities through its Program Planning Committee, the following should be noted as accomplished during 1962:

(1) The Study Section sponsored a Conference on Microbiological Quality of Foods (through a research grant) held in August 27-29, 1962, in Franconia, New Hampshire, under the chairmanship of Dr. Lawrence Slanetz. The purpose of this Conference was to consider the present status of our information on the microbiological examination and quality of foods. This included a consideration of indicator organisms, food spoilage and food poisoning infections and intoxications. Particular attention was given to research that is needed to resolve some of the problems related to microbiological food standards, food sanitation and food-borne diseases. Participants included highly recognized scientists from the Netherlands, Australia, England and Japan. Proceedings will be published by July 1963.

(2) The proceedings of the Study Section sponsored Conference on Epidemiologic Research in Occupational Health held in May 1961 has recently been published as a Special Supplement (October 1962) of the Journal of Occupational Medicine. In spite of the important role that occupational environment plays in the lives of almost half the population, disappointingly few applications have been made to the PHS for research in occupational health. The aim was, therefore, to create a working conference of people who would recognize the exceptional epidemiologic opportunities for research on the health of industry employees, and who would be able to contribute in one way or another to the initiation and progress of such research. The participants included epidemiologists and experts in other disciplines associated with occupational health. They represented industry, governmental agencies and universities.

(3) A paper on the Public Health Service Research Grant Program in Occupational Health, given by the Executive Secretary at the Third Inter-American Conference on Occupational Medicine and Toxicology was published in the July 1962 issue of Industrial Medicine and Surgery.

(4) Lengthy discussions have been held during the year by the Program Planning Committee on the possible need for establishment of a Journal of Environmental Sciences. The arguments for and against such a journal have posed difficult problems requiring careful consideration and further discussion.

It should be emphasized that (1) all recommendations of the Program Planning Committee are presented to the full membership of the Section for final consideration and action, (2) grants branch chiefs of all divisions of the Bureau of State Services (environmental health) have been invited to attend and participate in discussions at meetings of the Section's Planning Committee.

Experimental Psychology

During calendar year 1962, the Experimental Psychology Study Section reviewed 252 applications, of which 57 percent were given favorable recommendations. This compares with a total of 203 applications reviewed during 1961, of which 66 percent were recommended favorably, and with 1960, in which 184 applications were reviewed, 70 percent favorably. Thus, the total annual workload is rising, while the percentage of recommendations for approval is declining.

General Medicine

In the past year the review load of the General Medicine Study Section has increased approximately 20 percent, but has not been accompanied by a widening of the disciplinary spectrum of the applications assigned. Presently, the new normal load is not in excess of the Section's ability to deal with it.

The general scientific activity of the Section has resulted in planning, in conjunction with other units of NIH, a symposium on dermatology aimed at synthesizing fundamental and clinical scientific aspects of research in this field. The general subject of the symposium, hopefully the first of a series, will be keratinization. This Conference of invited participants will be held at the Arrowhead Conference Center of the University of California, in June 1963. The symposium and planned publication are supported by a grant from the National Institute of Arthritis and Metabolic Diseases.

The Section has also developed preliminary plans to hold clinical research workshops or conferences in areas of the Nation where adequate clinical institutions and competent clinicians are established, but where clinical research has not yet been developed. These plans will be developed further in 1963. Hopefully, a pilot workshop will be held, but the place and dates have not been set.

Genetics

During 1962 the Genetics Study Section reviewed 231 research grant applications, of which 154 were new proposals, 54 sought continued support and 26 were for supplements to current grants. Altogether 152 applications were recommended for approval, 46 for disapproval, and 13 were deferred for project site visits or for other additional information. This represents an increase of approximately 62 percent over the past four years in the number of applications reviewed annually.

A continuing aim of the Study Section's activities is to encourage the sound expansion of genetic research and to provide realistic assistance to this field. The first of a series of three volumes on genetic methodology, entitled "Methodology in Human Genetics," was published in March 1962. The volumes on "Methodology and Mammalian Genetics" and "Methodology in Basic Genetics" are in progress. The information for these publications was developed through three symposia, which were planned and carried out by the Genetics Study Section and completed in 1961, with financial support from the Division of General Medical Sciences.

During this year the Study Section has also focused attention on the potential genetic problem posed by widespread use of "chemosterilants". In collaboration with the Toxicology Study Section, an Information Session on Chemosterilants was held at the NIH on March 17, 1962. At this time a small group of experts from various disciplines was brought together to develop and exchange the available information on this subject. Of special concern to the Genetics Study Section is the possible mutagenicity of such compounds in higher animals, especially man, and the genetic implications of any widespread use of these chemicals. Future research development efforts of this Section will be closely related to these problems.

History of Life Sciences

The History of Life Sciences Study Section, formerly named History of Medicine, made notable progress during calendar year 1962. The Section reviewed nearly twice as many applications as in 1961 and appeared to physically find its full place within the Division, while at the same time, reflecting more fully the total scope of scientific interests of the NIH.

Study Section review of grants found 49 percent of the research grant applications and 80 percent of the fellowship applications being recommended for approval. Although the largest proportion of applications considered in the past two years have come from the National Institute of Mental Health and the Division of General Medical Sciences, four other institutes or divisions have also submitted applications.

Other than applications review, one of the most important projects undertaken by the Section was a one-day policy discussion on criteria for the award of NIH research fellowships and training grants in the field of the history of medicine. This meeting, held in conjunction with the regular Section meeting in May 1962, showed a considerable diversity of opinion as to the Study Section's actual mission as described by the name History of

Medicine Study Section. The findings of this meeting gave increased support to a proposal to clarify the Section's purpose by changing its name. Subsequently the name of the Section was changed in November 1962.

During 1962 also, the Section issued a joint invitation along with the National Library of Medicine to the American Association for the History of Medicine to hold its 1964 meeting in the Washington area. This invitation was accepted. Collaboration with Dr. George Rosen with respect to his NIH planning grant for a History of Health Research in the United States was started during the year. This activity is expected to increase steadily as the period of planning becomes one of actual research and writing.

Human Ecology

During calendar year 1962, the Human Ecology Study Section reviewed a total of 142 applications, of which 57 (40 percent) were recommended for approval. This compares favorably with the 30 percent of applications recommended for approval in 1961. Applications were reviewed from all Institutes and the DGMS and also from the BSS research and training grants staff. Twenty-four of the applications were from foreign countries, and ten of these were recommended for approval.

Three members left the Section in September and were presented with certificates of merit. Two new members, an epidemiologist and a sociologist, have joined the Section, bringing the present total of the Section to twelve members. Several more new members are expected to join the Section during the next few months.

The Section is particularly interested in methodology for demographic and epidemiologic investigations, and future plans include the examination of ways and means for encouraging the use of improved methods for community research. It is hoped to identify areas from all parts of the world with high potential for human population studies, and to encourage research in these areas.

Dr. S. Leonard Syme has now transferred to the Heart Disease Control Program, U.S. Public Health Service, San Francisco, and his place as executive Secretary has been taken by Dr. Bertie H. Woolf, who has been with the PHS since 1958.

Human Embryology and Development

During calendar year 1962, this Study Section reviewed a total of 286 applications requesting a total amount of $23,218,412. Of these, 153 applications in the amount of $7,847,624 were recommended for approval by the Study Section representing 53 percent of the applications reviewed and 32 percent of the amount requested.

In addition to the review of applications, the Study Section was engaged in the following activities designed to raise the standards of research activity in the field of human embryology and development and focus attention to problems considered of vital importance.

(1) A subcommittee of the Study Section formulated plans to hold an Institute in Developmental Biology in June 1963, at Madison, Wisconsin. An application was submitted for the purpose of financing this endeavor. Although the National Advisory Health Council fully concurred with the Study Section recommendation, it was found administratively impossible to activate this project, since no legislative authorization exists for the expenditure of funds for the purpose of motivating individuals to enter specific areas of activity.

(2) As in the previous calendar year, the Study Section again focused attention on the need to set up a mechanism whereby human embryonic tissue could be collected and made available to investigators working in particular fields of human embryology and development. It was pointed out that the best possible way to achieve this aim would be to collaborate with Japanese workers, since adequate embryonic tissues are available in Japan because of legalized abortion. However, no specific course of action was carried out in this direction.

(3) The Study Section sponsored a workshop on chromosome abnormalities which was held in conjunction with the annual meeting of the Teratology Society in Gainesville, Florida, on March 16 and 17, 1962. This workshop was extremely helpful to those embryologists who are interested in using newer techniques in studying the relationship of chromosome abnormalities to congenital malformations.

(4) At the April 1962 meeting, it was reported that malformations of thousands of babies in Europe were definitely linked to thalidomide, a new sedative marketed widely in Europe during the last two years. The Study Section pointed out that existing regulations in this country pertaining to the release of drugs for public use are inadequate since no requirements existed for mandatory testing of drugs for their effect on embryonic development. The Study Section felt that a subcommittee should consider this problem and make recommendations on what steps should be taken to point up the need for legislation in this direction. At the September meeting the subcommittee presented a report taking into account the events which led to new drug legislation, passed by Congress as the result of public attention. The report pointed out that, in spite of the new legislation, the task of the subcommittee did not seem finished and that more needs to be done in this direction. Dr. Saunders, Chief of the Research Grants Review Branch, DRG, reported to the Study Section that an Inter-Study Section Meeting was being planned to study this problem further. He informed the Study Section that members of the Toxicology and Pharmaceutical and Experimental Therapeutics Study Sections have already agreed to serve on this Inter-Study Section Committee and urged that the Chairman appoint several members of this Study Section to the Committee. The Chairman agreed to name two members of the HED Study Section to serve on this Inter-Study Section Committee.

Medicinal Chemistry A and B

During calendar year 1962, the Medicinal Chemistry Study Section reviewed 352 applications, 57 percent of which were recommended for approval. Most of the applications presented to this group have a large component of organic chemistry which may be synthetic, structural, mechanistic or involve studies of structure-biological activity relations. The Study Section is ever alert to the relation and value of the proposed studies to the health sciences.

The Study Section is concerned about the availability of reliable biological facilities for testing the many compounds prepared under grant support. Much research in this area never comes to fruition. Chemists start with a rationale for synthesis which may not be verified for lack of biological testing results. Biological activity needs to be put on a scientific basis and sound data should be available to allow prediction of biological response. An ad hoc Committee on Biological Testing, composed of members of the Medicinal Chemistry, Pharmacology and Experimental Therapeutics and Toxicology Study Sections, held several meetings and made the following three recommendations:

(1) Everything should be done to develop teamwork between chemists and pharmacologists. In order to open the lines of communication between members of these disciplines, the Committee agreed to prepare a booklet on biological testing facilities.

(2) Greater advantage should be taken of the research grants program to promote biological testing in pharmacology and other biology-oriented departments.

(3) The shortage of trained personnel might be lessened by the availability and award of postdoctoral fellowships to chemists seeking biological training.

Implementation of the first point has not been possible because of the present reluctance, due to patent problems, of the industrial pharmaceutical companies to continue to test compounds made under PHS grant aegis. The second recommendation is beginning to bear fruit through the receipt of research grant applications for support of modest research-related testing programs in academic departments of pharmacology.

The Study Section recommended that two parallel reviewing groups be formed in order to cope adequately with the increasing number of applications. The formation of Medicinal Chemistry A and Medicinal Chemistry B Study Sections was authorized and became effective October 1, 1962.

Mental Health A and B

Following two meetings of the Mental Health Study Section in calendar year 1962, the Section was divided into two parallel review groups designated Mental Health A and Mental Health B. Dr. Mordecai H. Gordon continued in the post of executive secretary for the A Section and Dr. Frank Freeman was appointed executive secretary of the B Section.

The two Mental Health Study Sections reviewed a total of 338 applications during the year, recommending 122 for approval, 196 for disapproval and 16 deferred. Four of the applications were reviewed informally and no recommendations were made.

In April 1962, the Section conducted a conference on "The Quantitative Analysis of Qualitative Data." The conference was held at Hillside Hospital, Glen Oaks, New York. Investigators attending the session presented clinical data in the process of being collected, and statistical consultants offered suggestions for quantifying this type of data.

Metabolism

Activities of the Metabolism Study Section during calendar year 1962 centered around three areas of interest:

(1) Continuation of the lipid distribution program sponsored by the National Heart Institute. For this program, the Lipid Advisory Committee acts as a subcommittee of the Study Section working in collaboration with the National Heart Institute (Dr. William H. Goldwater, Project Officer).

This committee of experts in lipid biochemistry advised the Division of Research Grants and the National Heart Institute on current deficiencies and supplies of lipid materials, and on possible approaches toward filling these needs.

The program continued to sponsor the supplying of either:
(a) Four mixtures of pure fatty acid methyl esters or
(b) Eight purified independent unsaturated methyl esters.

A continuing interest in obtaining other materials such as radioactive lipids for distribution was shown by the committee and it is probable that additional mixtures of methyl esters will soon be added to the program.

(2) Organization of a conference and stimulation of research on vascular complications in diabetes was considered by a subcommittee of the Section. A thorough analysis of the field by the subcommittee led to the suggestion that small blood vessel lesions may precede and may even underlie development of the more familiar manifestations of pancreatic diabetes.

Following discussion of this subject, the subcommittee prepared a conference grant application, subsequently approved. The National Heart Institute

and the National Institute of Arthritis and Metabolic Diseases will supply funds for the conference and the sponsoring institution will be the University of Texas Southwestern Medical School. The conference involving domestic and foreign experts in the field, will be held at Airlie House in Warrenton, Virginia, March 25-27 1963.

(3) The Metabolism Study Section is currently considering the need for preparation of reference standards of mucopolysaccharides, with particular attention focused on such materials as hyaluronic acid, several chondroitin sulfates and keratosulfate. Negotiations are now underway with commercial firms who may be competent to produce such reference standards.

Neurology A and B

For the past year (1962) the Neurology Study Section has reviewed an increasing number of applications, the total evaluated being about 305. Of these about 39 were project site visits. On August 24-27, inclusive, the Neurology Study Section held its last meeting as a single, undivided group. On September 1, 1962 it was split into Neurology A Study Section and Neurology B Study Section. Dr. Thomas O'Brien became Executive Secretary of the B Study Section while Dr. Pacita Pronove retained the same position for the A Study Section.

In conjunction with the August 1962 meeting the Neurology Study Section sponsored a one-day symposium on the "Mechanisms of Repetitive Firing of Cortical Neurons." It was held in the Medical School, University of Washington, which acted as host for the Study Section. Dr. Arthur A. Ward, Jr., Chairman and Professor, Division of Neurosurgery and a member of the Study Section was Chairman for this highly successful symposium. The enthusiastic response of the members to the symposium inspired the Section to continue to engage in programmed activities in the area of the neurological sciences. All these programmed activities will be organized and held under the combined sponsorship of the two Neurology Study Sections. However, for each programmed activity there will be one Study Section Chairman and one Executive Secretary. Recently, the Section has established a Steering Committee for Neuroanatomy of which Dr. Ray S. Snider is Chairman and Dr. Pacita Pronove, Executive Secretary. The other members of the Committee are:

(1) Dr. Ray S. Snider, Professor of Anatomy, Northwestern University
(2) Dr. Richard B. Richter, Professor of Neurology, University of Chicago
(3) Dr. Clement A. Fox, Professor of Anatomy, Marquette University
(4) Dr. David G. Whitlock, Professor of Anatomy, State University, Upstate Medical Center
(5) Dr. James W. Ward, Professor of Anatomy, Vanderbilt University
(6) Dr. A. Earl Walker, Professor of Neurological Surgery, Johns Hopkins University
(7) Dr. J. Francis Hartmann, Professor of Anatomy, University of Minnesota

The three ad hoc members included are:

Dr. Elizabeth C. Crosby, Professor, Department of Anatomy
University of Michigan
Dr. Charles H. Sawyer, Professor and Chairman, Department of Anatomy
University of California Medical Center
Dr. Walle J. H. Nauta, Chief, Department of Neurophysiology
Walter Reed Army Institute of Research

The Committee has had two meetings so far, the first at Nashville, Tennessee on October 7. This phase of organization of the program was attended by five Study Section members in addition to the two Executive Secretaries. The second meeting, in New York City on December 6, was attended by a fuller complement of members including two ad hoc members, Dr. Crosby and Dr. Sawyer. The research support from the Public Health Service for Neuroanatomy for fiscal year 1962 was reviewed and estimated as best as possible. The teaching of neuroanatomy and the prerequisites for a graduate degree in anatomy with neuroanatomy as a major subject was thoroughly discussed. The teaching of neuroanatomy to the medical students or in medical schools will be discussed at the next meeting, scheduled for this winter. The agenda also includes a symposium, conference or workshop.

Other projected programmed activities for both Study Sections include the following areas: Rheoencephalography, Viral Encephalitides, EEG and Computer Techniques, and Information Retrieval.

Nursing Research

During 1962, 41 applications were reviewed, of which 22, or 53 percent were recommended for approval. Nine site visits were made.

Some research problems in the nursing field require observation of interpersonal relations between the patient and nurse, and it is very difficult to obtain unbiased data of this kind. Investigators have begun to propose the use of closed circuit television (with or without kinescopes) so that more than one observer may view the same interaction, thus permitting reliability checks on the basic data of interaction studies. At the request of the Study Section, the Clinical Center generously arranged to demonstrate the use of television equipment in patient rooms, and to discuss the technical problems involved, for the benefit of the Study Section. In the opinion of the Executive Secretary, the Study Section would be justified in investing additional effort in exploring the potentialities and limitations of this technique as a tool for nursing research, and in making its assessment available to investigators.

Proposals were being received for review which involved evaluating the use of teaching machines or some other form of programmed instruction to teach either nursing or one of the disciplines basic to this field. At the request of the Study Section, Dr. Jack Edling, Senior Research Coordinator, Educational Media Branch of the Division of Statistical and Research Services, Office of Education, reviewed for them the status of research on programmed instruction, and the support available from the Office of Education for such research.

A research development committee has been appointed to consider how the Study Section might assist in developing research in the nursing field and to report to the Study Section for further discussion of this question. The Chief of the Research Grants Branch of the Division of Nursing has accepted an invitation to meet with this committee.

A meeting with representatives of each of the Institutes and Divisions which program extramural research was held by the Chairmen and Executive Secretaries of the Nursing Research and the Health Services Research Study Sections. The purpose of the meeting was to report results of a small jointly-sponsored conference held in 1961 to delineate patient care problems which need research, and there was endorsement of the need for research of the kind outlined, and for stimulation of high quality proposals in this area.

Pathology A and B

The Pathology A and Pathology B Study Sections act as separate units only during review sessions. From a staff and programming standpoint they act as a single unit.

The Pathology A Study Section reviewed 285 applications, largely in the fields of cardiovascular and other systemic diseases, approving 186 (65%) and disapproving 72 (25%). The average priority was 264. Project site visits were made in connection with the review of 27 projects. Of these 24 were approved.

The Pathology B Study Section reviewed 273 applications. About two-thirds of these were in the field of neoplastic disease. The rest were largely concerned with metabolic disorders. Of the total, 150 (55%) were approved and 144 (42%) disapproved. The average priority was 270. A total of 35 project site visits were made and 25 of the projects concerned were approved.

The major programming effort of the year for the two Sections was the Working Conference on Trout Hepatoma, held at the National Institutes of Health, April 11 and 12, to consider the epidemic of this disease in hatchery-bred fish. This was a closed meeting limited to about 30 participants. The meeting was organized by Dr. Philippe Shubik of the Study Section staff. The proceedings of the Conference have been given a limited distribution in mimeographed form. The conference was supported by grant CA-06627.

A brief symposium, The Preservation of Cells by low temperature methods, was included in the program of the Society for Experimental Pathology during the Federation Meetings at Atlantic City on April 15. This was a well attended presentation by four experts in the field representing the United States Navy, the Linde Company and Cambridge University. The meeting was organized by Dr. Averill A. Liebow and supported by the Division of Research Grants.

The second in a series of regional Departmental Chairmens Conferences is scheduled for New York City on December 7. Approximately 30 chairmen from departments of pathology in the northeastern United States and Eastern Canada will attend. The topics are the relation of research to other aspects of departmental organization, and the support of research through the National Institutes of Health. The conferences are essentially self- supporting.

The Pathology Study Sections have also cooperated with the Nutrition Study Section in the sponsorship of a series of working conferences on the development of a field of study of osteoporosis and dietary calcium levels. This activity, initiated at the behest of the World Health Organization, is still in the process of development.

Pharmacology and Experimental Therapeutics

The Pharmacology and Experimental Therapeutics Study Section is constituted to review research grant applications in the general area of drugs, their preparation, use, mode of action, metabolism, storage and excretion. Drugs are considered as substances applied to or administered to produce a desired effect in or on the body. These substances may be of exogenous origin or endogenous, if present in amounts greater than those normally occurring in the body.

Interests of the Study Section include the effects of drugs on: 1) nerves (conduction, transmission, etc.); 2) tissues such as bone, blood, smooth and skeletal muscle; 3) organs such as liver, kidney, cerebellum; 4) the organism as a functional unit such as animal and man; 5) its fate or disposition in the body as affected by these tissues and organs; and 6) clinical aspects of the use of drugs on patients with specific ailments. The Section is also interested in chemicals used in the treatment, diagnosis and prevention of disease.

A committee was appointed to look over the various research grants in the area of cardiac glycosides, to determine the need for a symposium to evaluate new approaches and new data currently becoming available. After hearing the report of this committee the Study Section agreed that it was premature to hold a symposium on this topic since the field is still in the early stages of development and most researchers are not yet ready to present data for a general discussion. Accordingly it was decided to postpone action in this area until methodology has become more definitive and individual investigators have had an opportunity to collect data.

Dr. John J. Burns, Dr. Lawrence Peters, and Dr. Frederick E. Shideman represented the Pharmacology and Experimental Therapeutics Study Section on the inter-study section committee on testing drugs in humans. This committee intends to hold several meetings to examine and review current methods of evaluating the clinical choice of drugs with emphasis on the safe use of drugs.

The August 30, 31, and September 1, 1962 Study Section meeting was held in Nashville, Tennessee, subsequent to the meeting of the American Society for Pharmacology and Experimental Therapeutics, which was held at Vanderbilt University. Members of the Study Section visited the Department of Pharmacology at Vanderbilt.

During the calendar year 1962 the Pharmacology and Experimental Therapeutics Study Section reviewed 329 applications and recommended 227 - or 69 percent - for approval.

Physiology

Physiology Study Section members made 24 project site visits during calendar year 1962 in connection with a total of 344 applications reviewed. The Section recommended 216 applications of those reviewed for approval; 95 were disapproved and 33 others deferred for project site visits or additional information.

The review of applications was the only formal activity engaged in by the Section during the year. Some time was spent in the course of each meeting informally discussing problems of policy, research needs and related subjects, however.

Dr. Hermann Rahn, a retiring member of the Section, was named president-elect of the American Physiological Society, and will be the eighth former Physiology Study Section member to serve in that capacity.

Psychopharmacology

During calendar year 1962 the Psychopharmacology Study Section approved several proposals based on the 1961 meeting on biological tests of schizophrenia. The Section held no conferences during the year.

Applications reviewed by the Section ran at a level similar to 1961, with 228 during 1962 compared to 220 in 1961 and 140 in 1960. Review of applications during 1962 resulted in 99 being approved, or an overall average of 44 percent of those reviewed.

Interest was shown by the Section members in projects showing promise of developing valid testing methods for differentiating effects on laboratory animals of biological substances drawn from pyschotics and non-psychotics.

Special

Since the beginning of the research grant program at NIH, there have always been some applications, the scientific merit of which couldnot be properly evaluated by any established reviewing body. These have been assigned to "Special Study Section" for individually designed review by an ad hoc group of experts in the research area or fields covered by the application. Thus "Special Study Section" covers no particular area and must remain flexible enough to cover any research area which falls outside the purview of the existing study sections, committees, or panels, or which cuts across the lines of two or more of them.

The areas of research which require special review have changed from time to time. New areas of research for which no reviewing group existed, have often grown until the number of applications in those areas justified the establishment of new formal reviewing groups. Examples of these areas are: Accident prevention research, Research in which establishment or maintenance of primate colonies was a primary factor, Russian translation, History of medicine, Toxicology, and Computer research.

During the calendar year 1962, 83 applications were reviewed, of which 55 were approved, 24 disapproved, and 4 deferred. This represents a disapproval rate of 30 percent.

Surgery A and B

The former Surgery Study Section was divided in October 1961 into Sections A and B. During calendar year 1962, Surgery Study Section A reviewed 207 applications of which 104 were recommended for approval, 101 for disapproval and 2 for deferral. Seventeen project site visits were made during the year by Section members. Surgery Study Section B reviewed 188 applications; 101 were recommended for approval, 86 for disapproval, and 1 for deferral.

To aid in determining the types of applications best referred to the Surgery Study Sections for review (particularly in relationship to those referred to the Cardiovascular and Hematology Study Sections), a report was prepared on the general and specific areas of interest dealt with by the Surgery Study Sections, conferences and symposia held, and publications which have resulted from Section activities.

In further consideration of recommendations of previous years, the two Surgery Study Sections developed a statement on supplementary funds for the research training of young surgeons. This statement was forwarded to the Director, NIH, on May 1, 1962, and was referred by his office to the Division of General Medical Sciences. Although a formal response to the statement has not been prepared as yet, the DGMS staff is keenly interested in this subject.

A Conference on Problem Areas in Shock was held at NIH on April 19 for the members of both Surgery Study Sections. Dr. Sam F. Seeley, Division of Medical Sciences, NAS-NRC, reviewed the actions and interests of the NRC Committee on Shock. This Committee had previously outlined the deficiencies which they believe exist with respect to research on shock in man. A number of representatives of other Study Sections and of several institutes attended the Conference and participated in the discussion.

At a joint meeting on September 7, 1962 the members of Surgery Study Section A and Surgery Study Section B discussed the number and kinds of projects and the amount of funds currently awarded for studies on the viability of the femoral head. During the one-year period, September 1961 through August 1962, NIH awarded approximately $250,000 in support of separate research projects dealing in part with this subject. Some of the Study Section members are of the opinion that in spite of the relatively large number of grants and the substantial amount of funds awarded over a period of several years for work in this area, little progress is being made. A committee, consisting of representatives of both Study Sections, was appointed to consider the need for a conference (1) to determine whether the approaches to the problem now being studied merit the present level of support and (2) to determine what other approaches might be explored.

A significant number of grant applications reviewed in 1962 dealt with research on prosthetic heart valves. Frequent reference is made in these applications to the results and unsolved problems which were delineated at the

Conference on Prosthetic Valves for Cardiac Surgery which was held in Chicago in 1960, under the sponsorship of the Surgery Study Section and with a grant support from the National Heart Institute. Thus it appears that the reference material resulting from this Conference and contained in the book entitled "Prosthetic Valves for Cardiac Surgery" published by the Charles C. Thomas Co., Springfield, Illinois, continues to serve a useful purpose to investigators working in this area.

Developments within the new NIH Division of Research Facilities and Resources as well as outside the Public Health Service may eventually minimize the usefulness of the brochure THE DOG IN MEDICAL RESEARCH (revised for the third time by the Surgery Study Section and published as PHS Publication No. 312 in 1961). Nevertheless, numerous requests for copies continue to be received from individuals and research institutions throughout the country.

During the year there was increased interest in the use of hyperbaric oxygenation in the field of surgery, particularly with respect to the treatment of trauma, shock, cerebrovascular disease and anaerobic infections. The Surgery Study Sections reviewed a number of applications dealing with the use of small pressure chambers for animal studies. Three broad, program-type applications from surgeons as the principal investigators involving the use of large clinical chambers were reviewed by a special advisory team. It appears that this new approach in surgery will be of substantial importance in the immediate future and that there will be increasing numbers of applications in this area.

Toxicology

The Toxicology Study Section continued to indicate its interests in the broad areas of environmental health. In keeping with its program interest, the spring meeting was held in Ames, Iowa, immediately preceding the "International Symposium on Food Protection" which was at the Department of Dairy and Food Industry, Iowa State University. Dr. John C. Ayres, a member of this Study Section and Professor of Food Technology at Iowa State, organized the symposium. Dr. Paul Cannon, chairman, and Dr. Harold W. Schultz, a member of the Toxicology Study Section, participated in the program. Subjects discussed during the three days included: Intentional Additives, Incidental Additives, Harmful and Pathogenic Organisms, and Microbial Toxins. The symposium was supported in part by a Public Health Service research grant, EF-39, from the Division of Environmental Engineering and Food Protection, Public Health Service. The symposium will be published in book form in the near future.

The "Symposium on Foods: Lipids and Their Oxidation" was published in September 1962. The book was edited by H. W. Schultz, a member of the Study Section and Head, Department of Food Sciences and Technology, Oregon State University. He had previously organized the symposium, held in Corvallis, Oregon, in September 1961, as the second of a continuing series of symposia on food. The earlier symposium and this publication were supported, in part, by a Public Health Service research grant, EF-28, from the Division of Environmental Engineering and Food Protection, Public Health Service.

The Toxicology Study Section, in cooperation with the Genetics Study

Section, sponsored an "information session on chemosterilants" which was held at the National Institutes of Health on March 17, 1962. Dr. James B. Kitzmiller of this Study Section and Chairman, Department of Zoology, University of Illinois, served as chairman. The purpose of this meeting was to bring together various groups working in this area for the mutual exchange of information and ideas. The various government and nongovernment scientists included chemists engaged in the synthesis of such compounds, field workers interested in the practical application of these substances, entomologists who discussed the theoretical aspects of these relatively new techniques on insect populations, geneticists who discussed the genetic implications of the widespread use of these chemicals, pharmacologists and toxicologists who emphasized the potential hazards to man and mammals associated with the use of such agents. Since the meeting was primarily designed to acquaint the participants with the present state of knowledge of the various aspects of this area of research, there was no intent to develop formal recommendations.

Dr. J. M. Coon and Kenneth P. DuBois represented the Toxicology Study Section on the inter-study section committee on testing drugs in humans. This committee intends to hold several meetings to examine and review current methods of evaluating the clinical choice of drugs with emphasis on the safe use of drugs.

During the year the Toxicology Study Section reviewed 132 grant applications and recommended approval of 87 (66%).

Tropical Medicine and Parasitology

Activities of the Tropical Medicine and Parasitology Study Section during 1962 reflected continued interest in encouraging better oriented, more inclusive interdisciplinary research in all fields of medicine in the tropics.

Notwithstanding the name of the Section, implying an interest limited geographically to the tropics, during 1962 applications were considered for research being conducted in the temperate and frigid zones, as well as the torrid zone.

A total of 283 applications were reviewed in the year, with 177, or 63 percent approved, 68 disapproved, 16 disapproved with advice to re-submit, and 14 deferred, some of the latter until project site visits could be made.

Visits to 15 project sites in five countries of Central and South America, with support totaling more than $970,000, were made jointly with representatives of the appropriate national advisory council and institutes from the Office of International Research.

Additionally, a two-week profile-study was made of the administrative, field and laboratory procedures of one grantee institution, the Gorgas Memorial Laboratory in Panama.

The Study Section continued to stimulate interest in symposia and panel workshops when it was believed such meetings would provide effective guidance and assistance in particular areas of research. The Section participated in

a Panel Workshop on Immunodiagnosis of Helminth Infections at the University of Maryland, with eight countries represented in November 1962.

Other meetings planned or contemplated for the near future are:
The First International Symposium on Animal Toxins, San Diego, January 21-25, 1963 with 21 countries to be represented
The First International Conference on Acarology, Colorado State University, Fort Collins, Colorado, September 3-7, 1963 with 25 countries to be represented

Also being considered for 1963-64 are sessions on Sylvan Rabies and a Fifth Conference on Research Needs in Tropical Medicine.

New members and grants associates were provided orientation at a special meeting, held annually in September, and were invited to audit the Study Section meeting held that month. Observers included personnel from the Division of Research Grants, divisions and institutes of the National Institutes of Health, various Public Health Service bureaus and other granting agencies attending the orientation proceedings. During 1962 there was an average of 17 observers for each Tropical Medicine and Parasitology Study Section meeting.

Virology and Rickettsiology

The Virology and Rickettsiology Study Section attempts to foster a balanced approach to research on the biology of, and disease or tumor production by, viruses and rickettsiae. The role of cell and viral constituents, such as nucleoproteins, (DNA, RNA, etc.), is of special interest to Study Section members.

The furtherance and stimulation of research is sought and application of knowledge already gained for the understanding of disease problems, their prevention, diagnosis and treatment, constitute major program goals.

Developments in the field of virology in 1962, much of it with grant support, continued to be significant and exciting as were the advances made toward the understanding of biochemical and biophysical processes at the cellular level. Also during the year, new techniques and tools were being implemented that promise further important discoveries.

The increasing amount of proposed research concerning a possible definite link between virus and cancer, reflected the current interest in studying this aspect of a most important disease problem. Reports of tumor induction in animals by common human (adeno) viruses provided even greater urgency to this study. Additionally, the development of comparative oncology; of new model systems for the study of the human virus-cancer problem, appeared to be bringing closer an eventual solution of that particular segment of the overall problem.

The occurrence of an epidemic of Arbovirus infections drew attention to this ever present hazard and the need for continued efforts aimed at solving this problem. Proposals for practical application of research, as in environ-

mental sanitation and control programs, are currently being received and are expected to increase in the future.

On the other hand, proposals to study host factors in the host-parasite-environment complex have appeared infrequently. Viral hepatitis, also, remains an unsolved problem and one in which minimal grant research activity has occurred.

Applications reviewed by the Study Section during calendar year 1962 totaled 287 with 64 percent recommended for approval. Approximately 24 to 33 percent of the proposed research was directly cancer-oriented with the remainder distributed between basic studies, categorical diseases or preventive aspects of viral or rickettsial diseases.

The Study Section stimulated and sponsored The International Symposium on Newer Respiratory Virus Diseases, held in Bethesda in October 1962. Purpose of the symposium was to consolidate accumulated knowledge, provide for an interchange of thinking and to point out gaps and areas of needed research concerning newer respiratory virus diseases. The Section was also involved in The Symposium on Bovine Leukemia at the University of California in April 1962. This symposium represented support of the comparative cancer approach, another area being stimulated by the Section. Supportive efforts on model systems ranged from studies of cell viruses of Lucke virus in frogs, through systems of mice, chickens or dogs, to sub-human primates. The imminent availability of germ-free mice from commercial sources, and the numerous research projects now under way with this technique, essential to infectious disease or oncologic research, is also an outgrowth of efforts of the Study Section.

Looking to the future, the Virology and Rickettsiology Study Section plans to further the consolidation and application of knowledge through the conference mechanism. Plans call for An International Conference of Avian Tumor Viruses, and a conference on the Emergence of Newcastle Disease.

Study Section support will also be given a symposium to consider viruses, nucleic acids and cancer, planned for February 1963, at the M. D. Anderson Hospital in Houston, Texas. Scheduled for the early part of 1963, also, is a meeting to explore the needs, methods and applications for virological research in environmental sanitation. The Virology and Rickettsiology Study Section is presently seeking other areas of interest to be considered during the 1963 calendar year.

Visual Sciences

The Visual Sciences Study Section held its first meeting in September 1962, following division of the former Sensory Diseases Study Section in July. The new Study Section reviewed 43 applications, of which it recommended 28 for approval, or 65 percent.

Several subcommittees had been established by the Sensory Diseases Study Section for the purpose of planning conferences on 1) normal visual perception, 2) the crystalline lens, and 3) differences in inflammatory reactions in vascular and avascular tissues. The membership of these subcommittees has been

augmented by the appointment of new members from the new Visual Sciences Study Section.

The activity of a subcommittee studying the problem of information retrieval has resulted in the submission of a research grant application requesting support to investigate the suitability of existing systems of retrieval.

Scope of Activity

The Branch's activities, related to the management of the PHS grants programs, are directly involved in the formulation and implementation of PHS grant policies, procedures and practices for research projects, training grants, program projects, clinical centers, general research support, and health research facilities grants. The branch exercises influence on all aspects of administration (exclusive of scientific consideration) of the institutes' grant programs, and also services other divisions of the Public Health Service.

General Responsibilities

The Branch facilitates the administration of the PHS grants programs in six principal ways:

(1) It provides leadership in policy development and interpretation.

(2) It coordinates and oversees most of the fiscal management policies and requirements applicable to grants,

(3) It provides the mechanism for implementing payments and, to a limited degree, controls grant funds through verification, detail recording and reporting analysis.

(4) By reason of its role in the area of fiscal policy, it is one of the instruments by which the institutes and divisions and the grantee institutions execute their financial plans.

(5) It serves as a sounding board for over 1200 grantee institutions on matters pertinent to the management of grants.

(6) It speaks for the National Institutes of Health on intergovernmental committees and before university associations on matters of mutual interest in the administration of grants programs.

1962 Activities

1962 has been a year of increased emphasis on the importance of grants management activities and resultant change for the Grants Management Branch. This emphasis is directly attributable to the circumstances which have emerged from the rapid rate of growth of the NIH programs over the past few years. In a letter to the PHS Surgeon General dated April 6, 1962, NIH Director Dr. James A. Shannon said:

"In this development (the rapid development of NIH programs over the past 5 years), the complex problems and issues surrounding

the administrative and management aspect of our program expansion have not received parallel emphasis."

The Fountain Committee Hearings highlighted the need to strengthen the administration of the grant programs. Again, quoting Dr. Shannon's letter to the Surgeon General:

> "However much we may differ from the specifics of the Fountain Committee's viewpoints, and its suggested corrective approaches, there are sufficient instances of error, limitations, and inadequacies in our actions or arrangements to warrant prompt and extraordinary effort on our part to assess, reaffirm or modify both the generalities and specifics of our grant administration process."

The many important changes in this Branch that occurred in 1962 are directly attributable to the increased emphasis on grants management. On June 29, 1962, the Interbureau Directing Committee, under the direction of Dr. David E. Price, Deputy Director, NIH, issued a report entitled "Administrative Changes in the PHS Research Grants Programs." This report recommended 13 functions to be performed "by a grants management organization with Public Health Service-wide responsibilities.":

1. Functions involving relations with individual grantee institutions where uniformity of interpretation is paramount.

   a) Negotiate agreements with grantee institutions to establish fund control systems.

   b) Make periodic visits to grantee institutions to see how these systems are operating.

   c) Make periodic analyses in grantee institutions of such matters as hospital costs, and salary policies and practices.

   d) As requested, provide consultation on grants management matters to grantee institutions and to awarding institutes and divisions.

2. Functions involving development of uniform policies and practices for the Service.

   a) Provide the focus for the establishment of financial policies with respect to grants, e.g., salary, hospital costs, renovations, etc.

   b) Make studies of management problems inherent in new support programs before these programs are established.

c) Accumulate case histories and develop a body of well-documented precedents for purposes of policy development and interpretation.

d) Provide Institutes and Divisions with minimum standards and guidelines for reviewing grant budgets, expenditure reports and related documents.

e) Provide assistance with and make recommendations on the disposition of proposed audit exceptions.

f) Participate in development of grants policies and procedures.

3. Functions relating to training and information designed to inform staff of general practices and policies:

a) Notify all Public Health Service Institutes and Divisions of precedent-setting decisions on a regular, formal basis.

b) Develop training materials and conduct training programs for new Public Health Service employees and grantee institution officials.

c) Conduct seminars for Public Health Service and grantee institution officials when new regulations or policies are promulgated or new support programs installed.

This report had a major effect on the Grants Management Branch in 1962 and will have far reaching effects in the years to come.

Among the most important changes in 1962 were:

1. Personnel Changes - Mr. Clarence Lowe, who had been Chief of the Branch since its inception was made Assistant to the Division Chief for Extramural Grants Administration. Mr. Sidney B. Cohen, Assistant Branch Chief, became Branch Chief, and Mr. Calvin B. Baldwin, Jr., became Assistant Chief. During the fall, four Grants Management Specialists who are skilled in administration and financial management were added to the staff to give further strength to the central grants management effort.

2. Transfer of the Grants Audit Section - Effective June 1, 1962, Dr. Shannon approved the transfer of the Grants Audit Section to the Financial Management Branch, Office of Administrative Management. The transfer was made as a result of a report on audit of grants prepared by the Office of Management Policy, DHEW, Office of the Secretary. The recommendation to transfer this Section from GMB was based on the "principle that an audit unit should not report directly to the official

immediately responsible for the administration of the program being audited."

3. Formal Publication of Grant Regulations and Procedures - Of key significance to the effort to strengthen the administration of grants were actions taken during 1962 to compile, publish and distribute regulatory, policy, and program information. For the first time, regulations were drafted for research project grants to be published in the Federal Register. The Grants Management Branch was responsible for proposing the establishment of a "Manual to Facilitate Administration of Research and Training Grants" and providing the basic draft on the section on Research Grants. This first section of the Manual was distributed to all grantee institutions in December 1962, following careful review and improvement by numerous individuals and committees throughout the Public Health Service.

4. At the end of 1962, work was in progress on the following major areas: The Training Grants Section of the Manual, development of a basis for determination of hospitalization costs applicable to specific research grants, the establishment of a policy on fund control within grantee institutions, a study of the payment procedure and reports of expenditures, and procedures for carrying out the new 20% indirect cost policy.

Grants Audit Section and Policy, Procedure and Audit Review Section

The work of these two sections is essentially the same as reported in 1961. Emphasis has been placed on improving the procedures of the sections to enable them to handle an increased workload without a corresponding increase in staff.

Forecast for the Future

The intensified interest in an emphasis upon grants management will inevitably result in many changes in the future. Of the most immediate concern are:

1. Defining the role of central grants management and its relation to grants management in the Institutes and Divisions and improving communications between the two.

2. Collaboration with the Policy and Procedure Office in preparing remaining sections of the manual.

3. Improving communications with grantee institutions and other Government granting agencies through seminars on grants management and by more active participation in regional meetings of the associations of college and university business officers.

4. Implementation of the Price Report recommendations, including the establishment of a pilot field operation for certain grants management activities, the accumulation of case histories and a body of well-documented precedents for purposes of policy development and interpretation, etc.

STATISTICS AND ANALYSIS BRANCH

Administration of the Statistics and Analysis Branch during 1962 continued to be under the direction of an Acting Chief who simultaneously served as Assistant Chief of the Division of Research Grants. The Branch consisted of the Design and Analysis Section and the Statistical Processing Section until November 1, 1962, at which time the Design and Analysis Section was transferred to the Office of Program Planning, Office of the Director, NIH.

A number of basic changes have been put into effect during the year. First, transition from a limited electric accounting machine procedure for data accounting and management to electronic processing was accomplished in two stages: (1) IBM 650 operation, and (2) Honeywell 800. Second, in late FY 1962, it was decided to include data for all granting units of the Public Health Service. This decision added new responsibilities and greater volume and complexity to the activities of the Branch. Third, additional new programs during FY 1962 made it necessary to create sub-categories for the resultant data. Examples of these additional programs are: (1) general research support grants, and (2) career development awards.

Continued studies of data requirements on the extramural grant and award (EGA) programs have been made during 1962. The concept of core data has been formulated to include those essential for over-all information to the Office of the Surgeon General and offices of the Bureau Directors, and for complete reporting of administrative actions. However, since each granting Institute and Division within the Public Health Service has unique data requirements, provision has been made in planning the over-all grants and awards data systems for subsystems that will fit the over-all PHS core data system.

The Branch has increased its capacity for developing programming procedures on the Honeywell 800 (1) through employment of programmers dedicated to the specific problems of the EGA data and (2) through a research contract between the Division of Research Grants and George Washington University which began in June 1962. This contract has greatly assisted progress towards improved usage of H-800 in processing EGA data.

Each granting Institute and Division was requested by the Division of Research Grants to designate an individual to represent it on a newly-formed panel known as the EGA Data Panel. This panel, which met for the first time in August, acts as an advisory body to the Division of Research Grants on data systems and subsystems. Each member of the panel provides liaison between his Institute or Division and the Statistics and Analysis Branch.

Additional positions in the Office of Program Planning, Office of the Director, NIH, have resulted during the year in improved liaison, direction and advisory services between that office and the Division of Research Grants. Improved procedures have also been provided for active guidance in the PHS grants and awards data management.

For several years, staff members from the Management Policy Branch of the Office of the Director have acted as consultants to the Division of Research Grants in studies for improvement of the EGA data management procedures. One such study dealing with competing applications for research grants has been advanced during 1962 to the stage of early operational tryout.

Future plans:

Development of a reasonable optimal network of subsystems for EGA data which would provide (1) compatibility, and (2) multilateral and integrated operational accomplishments, requires an organizational concept and functions of a much higher order than those previously encompassed by the Statistics and Analysis Branch. Plans for the development of the reconstituted Branch was initiated in February 1962 and are currently being formulated for activation under the title, Data Systems Branch, DRG. The reconstituted Branch would have increased responsibility for (1) EGA systems analysis, (2) integration and control of coding structure for core data, (3) inter-relationship of data selection, editing and coding performed in offices decentralized in these functions from the Branch, (4) repository for all electronic data processing programs utilized on core data.

Reports on the 1962 activities of the two Sections follow:

Design and Analysis Section

Reports and Studies completed during the year are as follows:

(1) Survey of Expenditures under NIH Research Grants in Fiscal Year 1960.

(2) Relationship of Study Section Membership to Study Section Approval Rates of Research Grant Applications. (An investigation of possible "university influence".)

(3) Summary of NIH Awards by Type of Extramural Program to Institutions of Higher Education in the U.S. and Possessions - 1959 to 1961.

(4) Fiscal Duration of NIH Grants (a study of attrition and survival of NIH Research Grants from 1946 to 1961.)

(5) Trends in Large Grants, Multiple Grants and Numbers of Grantees under NIH Research Awards, 1955 to 1961 (an inquiry into the distribution of Principal Investigators under NIH grants in terms of grant sizes and multiple grants.)

During 1962, work proceeded on a Survey of Personnel Participating in NIH Research Grants and will continue through 1963. Planning for this survey began in late 1961 and has been a major activity of the Section to date. Questionnaires were sent to a subsample of Principal Investigators in July 1962; the second subsample was queried in October and a third is planned for March 1963. Work is proceeding on the conventional operations of survey management, coding, card punching, etc. The purpose of the survey is to probe the attributes and characteristics of all participants on active NIH research grants. The distribution of characteristics, and especially the discipline profiles of this group, is of prime consideration. A secondary goal is information relevant to the quantity and depth of research training received under the NIH research grant programs.

Project Control, NIH

This function, which was termed Reports Control, prior to January 1962, is a responsibility of the Section. Under authority of a memorandum from the Surgeon General, January 1962, the scope of the service was greatly expanded in technical directions over and beyond its former forms clearance aspect. In cooperation with PHS, HEW and Bureau of the Budget all NIH projects involving data gathering from the public are now being examined and cleared through this Section.

Statistical Processing Section

Introduction

The Section, with four administrative units, continued throughout 1962 to collect, compile, analyze and publish statistical data relevant to all extramural grants and awards programs of the Public Health Service. Activities included the processing of administrative information, designated as "core" data, for 45 distinct sub-programs grouped within 5 major research and training categories -- research projects, center programs, training projects, fellowships, and research career awards. Over 20,000 active grants and awards, transacted by 22 institutes and divisions, were included in the central statistical file.

Development of Integrated Data Systems and Reports for Extramural Programs, PHS

The plan for DRG data systems provides for a single master source of information "core data" to be stored in magnetic tape, thus establishing a central consolidated file readily available for high speed search and retrieval. Punched cards now serve as input to the magnetic file. Paper tape and other input devices are planned for the future. Approximately one million cards were prepared for the 1962 magnetic file.

Core data relating to extramural programs come from a variety of source documents, and vary in complexity to serve a variety of uses. Since information often arises, or is first received, within an Institute or Division, a major innovation this year was to establish decentralized data-capture activities closest to the origin and management of source documents. The Career Development Review Branch of the Division of Research Grants initially implemented this plan. A similar but more limited activity is now being developed in the Research Grants Review Branch, DRG, following plans developed from studies by personnel from Management Policy Branch, OD, NIH. Future development of this concept provides for similar adaptation by other grant and award units of PHS. Extensive systems analysis and model testing is well under way. The eventual goal is to develop core data for an integrated data system responsive to individual requirements of institutes and divisions, as well as for the over-all needs of the Office of the Director, NIH, and the Public Health Service.

Program Progress

For 1962, the central information system was expanded to include data for all programs administered by PHS through the Bureau of State Services. Thirteen additional divisions thus formed a total network of 22 institutes and divisions reporting extramural core data. These data are represented in varying complexity for subprograms. They range from 28 to 38 variables of information for health research facilities and research grants to 66 and 80 variables respectively for training grants and fellowship awards. During the year, major attention was given to the alignment, definition and content of core data to be integrated from subsystems of the total extramural program. Revised policies, changes in operating programs, and the introduction of new programs, necessitated many revisions in existing data collection and processing procedures.

In brief, the Section devoted its major efforts toward:

(1) Continued development of a comprehensive coding system to capture core data from documentary sources on all grants and awards of PHS.

(2) Continued development of uniform instructions and standard procedures for processing data relevant to specific subsystems of the PHS extramural program.

(3) Preparation of complex machine specifications, and technical computer programs and routines, to facilitate data accessibility and information retrieval.

(4) Preparation of a variety of compilations, analyses and special summaries in answer to the comprehensive interests of a wide community of users in PHS and other Federal, non-Federal and public agencies.

Reports

The most widely known reports prepared in the Section are the annual publications listing PHS grants and awards by State and Institution. Summaries of data for FY 1962 will appear in five volumes and will include all PHS grants and awards, not just the listings of NIH grants and awards as in previous years.

The following list presents the contents of these publications:

Part I - Research Projects

Table I - Grant Totals for Research Projects, by Supporting Institute or Division
Table II - Research Projects - (Listing of Grants by Geographic Area, Grantee Institution and Principal Investigator)
Table III - Summary, Extramural Research Program - (Totals for Grantee Institutions by Supporting Institute or Division)
Table IV - Summary, Extramural Research Program - (Totals for States or Countries by Supporting Institute or Division)

Part II - Training Grants, Research Fellowships, Traineeships and Research Career Awards

Table I - Totals for Extramural Training Programs, by Supporting Institute or Division
Table II - Graduate Training Grants - (Listing of Grants by Geographic Area and Grantee Institution)
Table III - Undergraduate Training Grants, (Listing of Grants by Geographic Area and Grantee Institution)
Table IV - Summary of Extramural Training Grants, Graduate and Undergraduate - (Totals for Grantee Institutions by Supporting Institute or Division)
Table V - Summary of Extramural Training Grants, Graduate and Undergraduate - (Totals for States or Countries by Supporting Institute or Division)
Table VI - Traineeship Awards - (Listing of Trainees by Geographic Area and Sponsoring Institution)
Table VII - Fellowship Awards - Listing of Fellows, Including Student Part Time Fellowship Grants, by Geographic Area and Sponsoring Institution

Table VIII - Research Career Awards - Listing of Awardees by Geographic Area and Sponsoring Institution

Part III - Construction Programs - Health Research Facilities, Cancer Research Facilities, Hospital and Medical Facilities

Table I - Grant Totals for Health Research Facilities, Cancer Research Facilities and Hospital and Medical Facilities Construction Programs

Table II - Health Research Facilities (Listing of Grants by Geographic Area, Grantee Institution and Responsible Official)

Table III - Cancer Research Facilities - (Listing of Grants by Geographic Area, Grantee Institution and Principal Investigator)

Table IV - Hospital and Medical Facilities Construction Programs (Listing by Geographic Area and Grantee Institution)

Table V - Summary, Health Research Facilities, Cancer Research Facilities, Hospital and Medical Facilities (Totals for Grantee Institutions by Supporting Institute or Division)

Table VI - Summary, Health Research Facilities, Cancer Research Facilities, Hospital and Medical Facilities, (Totals for States by Supporting Institute or Division)

Part IV - Health Services Formula and Project Grants

Table I - Grant Totals for Health Services and Health Service Studies and Demonstrations by Program

Table II - Health Services Formula and Project Grants (Listing of Grants by State and Grantee Organization)

Table III - Allotments to Interstate Agencies for Water Pollution Control

Table IV - Summary, Formula and Project Grants (Totals by Region, State and Program)

Part V - Summary Tables Summarizing Data in Parts I through IV. The exact content of this volume has not been determined at this time.

I. Origin and Functions of the Career Development Review Branch

CDRB has now operated for almost two years as the coordinating unit for of NIH's extramural training award programs. Reorganized in March 1961, it retained the functions for predoctoral, postdoctoral, and special fellowships as well as for those programs that now constitute the research career program, and acquired the responsibilities of the Training Section, formerly a part of the Office of the Chief, DRG. In absorbing this section, CDRB took on the responsibilities delegated to DRG by the NIH Director's Office on February 10, 1960, to serve as the agent for central management of training grant and award programs.

CDRB functions therefore include (1) review of applications for predoctoral, postdoctoral and special fellowships, graduate training grants, and research career program awards for acceptability and assignment to the appropriate Institute; (2) scientific review and evaluation of the above types of fellowship applications through committees of academic research scientists, with staff assistance to these committees; (3) development and implementation of uniform policies and procedures for central management of training award programs; (4) capture and storage of data on applications and awards in the programs for which CDRB has a coordinating responsibility, and in the international postdoctoral fellowship, direct traineeship, undergraduate training grant, postsophomore fellowship, and student part-time research fellowship programs; (5) periodic analyses of current professional activities of former fellows and trainees and other studies important to health research training.

II. Increased Scope of Administrative Management Responsibilities

In Fiscal Year 1962 the Branch processed 4,746 fellowship applications, compared with 4,280 in 1961 and 1,220 graduate training grant applications, compared with 1,056 in 1961. Applications for the research career program, organized in 1962, numbered 1,133. With this heavier workload and an increase in number of new branch personnel, CDRB is reoriented its approach to administrative management. The number of assistant branch chiefs has increased from 2 to 3 so that there is now one for each of the following programs: fellowships, training grants, and the research career program. CDRB's Project Control Section, which is responsible for receipt, assignment, and other phases of control of fellowship, training grant, and research career program applications, was reorganized and put under the guidance of a project control officer who was given an assistant to concentrate on application assignments. The number of fellowship review panels has grown from 10 to 12. In addition, an executive secretary has been appointed to assist in the review of fellowship applications not assignable to existing panels. Further, more attention is being devoted to in-service training of branch personnel. Since current automatic data processing equipment has proved inadequate, the rental of more modern IBM equipment has been requested in view of CDRB's responsibility for data retrieval, storage, and current reporting as well as for all input into NIH's Honeywell-800 for all NIH extramural training award programs. Such

machinery will also facilitate capturing data from the forms reporting appointment of trainees by grantee institutions under NIH graduate training grants.

III. Revision of Publications to Inform the Public of Policies on Fellowship, Training Grant, and Research Career Programs

The branch has taken leadership in reorganizing and updating statements to inform the public on the policies governing those extramural training award programs which CDRB coordinates. This was first done for fellowships in 1961.

In December 1961, the branch initiated a draft of policies covering undergraduate and graduate training grant programs of NIH and coordinated this with the Institutes, DGMS, and other units concerned. Early in 1962, after DRG's Policy and Procedure Office was operating, a later CDRB draft was coordinated with such units through PPO. This brochure of "Administrative Policies Governing Training Grants of the National Institutes of Health" was published May 1, 1962 and disseminated to grantee institutions.

There are now in process of revision by CDRB (1) the NIH research career program policy statement and (2) a statement of policies governing predoctoral, postdoctoral, and special fellowships to incorporate predoctoral fellowship allowance changes and to encompass all PHS fellowships, whether financed from NIH or BSS appropriations.

IV. Policy Changes Initiated by CDRB

A. Changes effected

1. Predoctoral fellowship allowances

Effective July 1, 1962, PHS delegated to training institutions within the United States most of the supervisory functions relating to PHS predoctoral fellows' day to day activities. Each institution training PHS predoctoral fellows has appointed a coordinating official. Although the fellows continue to be selected by PHS, the training institution receives funds directly from PHS to provide stipends and allowances to predoctoral fellows. Each such institution is provided, in addition, a predoctoral fellowship allowance of $2,500 per year per predoctoral fellow. This is in lieu of tuition and fees and the former supply grant, and is intended to strengthen the research training provided to these fellows. To facilitate this change, CDRB staff during FY 1962 visited each university in the United States which trains PHS predoctoral fellows.

2. Citzenship requirements of trainees receiving stipends undergraduate training grants

The variations in the policies of DGMS and the Institutes on the citizenship of trainees drawing stipends under graduate training grants had been discussed by DRG's former Training Section with the Institutes and DGMS in January 1961. To settle this question in the training grant policy statement, CDRB brought these variations to the attention of the Office of International Research. OIR, working with CDRB and PPO, established uniform requirements for all Institutes and DGMS in this area as of June 15, 1962. Now, except under NIMH- and NIDR-supported programs (which require of those drawing stipends either United States citizenship or the filing of a Declaration of Intention to become a U.S. citizen), only unusually well qualified foreign nationals (non-Declaration filers) who have reasonable assurance of a research career opportunity on completion of training may be appointed as trainees. Such foreign trainees must be appointed under a program in which the program director has anticipated the need for stipends for foreign nationals and, on the basis of information furnished to NIH as to the purpose of providing stipends for foreign nationals, the criteria and mechanism to be used in their selection, the nature of training proposed for them, and the maximum number of foreign trainees anticipated, has secured NIH approval. If the NIH-supported training program has not been approved for appointment of foreign trainees, each such appointment must be approved in advance by the sponsoring Institute or Division.

3. Equipment purchased with training grant funds

Because under Public Law 85-934 PHS does not have the discretion in training grants that it has with research grants to vest title in the grantee institution without further accountability to the Federal Government for equipment purchased with grant funds, CDRB, working with other organizational units concerned, has recommended amendment of this law. The purpose is to apply the same policy to equipment purchased with either research or training grant funds.

B. Changes Under Consideration

1. National ceilings for NIH contributions for stipends under graduate training grants

In 1961, CDRB had proposed the possible establishment of national ceilings on NIH contributions for stipends under graduate training grants and a closer correlation between stipends paid in the same field of training under pre-

doctoral or postdoctoral fellowships and graduate training grants. Further attention was focused on this matter in 1962 and CDRB now plans to survey at selected universities stipends and salaries paid to graduate students under a wide variety of programs in order to gather further evidence on (1) the possibility that the present stipend policies for training grants need re-direction, (2) appropriate stipend levels for fellowships, and (3) the local relationship between these two programs.

2. Change in loyalty statement requirements under fellowship and research career programs

Public Law 87-835, passed in October 1962, changed requirements on loyalty affirmations in connection with certain training award programs of the National Science Foundation and the Office of Education. This law removed the disclaimer affidavit, but retained the loyalty affirmation requirement. CDRB has proposed changes in its regulations to conform to a practical extent with this policy set for NSF and OE.

V. Progress in Procedural Coordination

A. Fellowships

When the predoctoral fellowship allowance was established, a series of procedural changes (methods of payment, revision of forms, more frequent and concentrated liaison with officials of the training institutions, etc.) became necessary. The Institutes will be informed of new procedures through the dissemination of a manual which is being prepared by CDRB.

B. Graduate training grants

In 1962, CDRB, working with the Institutes and DGMS, revised Form PHS-2271, the statement of appointment of an individual who draws financial benefit from an NIH graduate training grant. This revision of the form and instructions will facilitate a more uniform collection of comparable data on indirect trainees. Such data are essential to quantitative evaluations of our training grant investment.

Plans are underway to compile a procedures manual in order to have comparable procedures followed by the Institutes and DGMS in processing training grant applications. Further work is planned on the revision of the training grant application form. CDRB plans also to develop a uniform procedure for facilitating the filing and processing of applications for renewal of graduate training grants.

C. Research career program

Based upon a year of actual experience in processing research career program awards, CDRB has developed a revision of the RCP application form and instructions. It expects by the end of 1962 to have compiled a procedures manual for this program which will be comparable to the proposed procedures manual on training grants and to the well-established manual for fellowship administration.

D. Training awards in general

Because of changes in program interests of the present Institutes, the impending creation of new Institutes, and the burgeoning of new training programs in BSS, CDRB plans to revise its handbook of referral to facilitate assigning applications for fellowships, graduate training grants, and research career program awards among PHS Institutes and Divisions.

VI. Special and Continuing Analyses of Training Award Programs

CDRB has worked closely with the Institutes and DGMS to complete early in 1963 the first NIH-wide study of current professional activities of trainees supported under graduate training grants.

CDRB has also initiated a pilot study of the characteristics of RCP awardees and their sponsoring institutions and plans further studies to compare FY 1963 with FY 1962 awardees.

The branch plans to publish in 1962 its completed study of "Undergraduate Origins, Location of Training, and Size of Institution Attended by Recipients of NIH Predoctoral, Postdoctoral, and Special Fellowship Awards, Fiscal Years 1957-1960." This analysis examines individual universities and geographical areas that have provided the undergraduate training of substantial numbers of NIH predoctoral, postdoctoral, and special fellows. It also weighs the significance of the size of the undergraduate institution in producing future NIH fellows.

Increasingly CDRB is looked to as the source of data on policies, procedures, and statistics on all extramural training support programs of NIH. In addition to continuing its annual listings of fellowship and RCP awards, CDRB devotes an increasing proportion of its time to meeting special requests for comprehensive data -- for example, requests from the Office of the NIH Director, the Budget Bureau, the Office of Scientific Adviser to the Secretary of State, the House Education and Labor Committee.

VII. Significant Professional Meetings Participated in by CDRB Staff

Professional meetings in which CDRB staff members actively participated include: the two annual Federal Fellowship Administrators meetings; the conference held in October 1962 at the call of a subcommittee of the deans of

liberal arts colleges of the Big Ten and the University of Chicago to discuss the effect of late faculty fellowship awards on replacement of faculty planning sabbatical leave; the conference held at Columbia University in November 1962 of representatives of certain training institutions, the Office of Education, NSF, and NIH on problems of administering financial aid for graduate students; the March 1962 meeting of the American Association of Anatomists; the November 1962 meeting of the Midwest Association of Anatomists; the April 1962 meeting of the American Pharmaceutical Association; the October 1962 meeting of the American Society of Tropical Medicine and Hygiene; the October 1962 meeting of the American Public Health Association; the September 1962 meeting of the American Sociological Association; the December 1962 meeting of the American Association for the Advancement of Science; and the second annual meeting of the Council of Graduate Schools in the United States.

INTERNAL OPERATIONS BRANCH

The Internal Operations Branch provides a variety of administrative services and housekeeping functions for Division personnel, as well as certain central services, and furnishes the program materials for the extramural programs of other Divisions and Institutes.

The Branch is organized as follows:

Office of the Chief - The Office of the Chief provides overall supervision of all Branch activities, and maintains liaison with other Divisions and Institutes, in addition to performing specific functions, such as space planning and forms clearance control. During the past year, over 60 requests for telephone changes were submitted which involved installations from a single instrument to a very complex installation for an entire building. Approximately 200 work requests were prepared and processed to the Plant Engineering Branch requesting services varying from installation of a blackboard or bulletin board to major renovations. During the past year, the Office of the Chief acquired the services of a Forms Analyst to assist in the preparation and handling of the various extramural program forms and Division administrative forms. In addition, a full-time bookkeeper was employed to take care of the thousands of travel vouchers processed through the Branch.

Office Services Section - This section performs a variety of functions and duties, particularly those concerned with procurement, property, supply, and documents relating to these activities. During the past year, this section has performed various types of service requests from opening a stuck file drawer to completing what almost would constitute a major renovation of an office. For example, this section has issued on an average of approximately 5,000 application forms per month. They have wrapped and mailed an average of over 2,500 packages per month. They have received and installed approximately 50 pieces of furniture and equipment per month, not to mention several hundred miscellaneous service requests, relocating office furniture, etc. In addition, this section is also responsible for the operation and maintenance of the various types of office copying machines, which during the past year have produced uncounted thousands of copies of documents of all types.

Special Services Section - This section is primarily concerned with providing special services such as general typing, extra clerical and typing help upon occasion, and controlling the flexowriters used in the general letter typing operations, as well as those used in the data capture operations of an automatic data processing function. This latter function has been proved and tested repeatedly, and in the future, it will provide an excellent means of obtaining information from all research grant applications. During the past year, approximately 200 jobs were performed on the two letter-writing flexowriters, ranging in size from 10 to over 800 letters per job.

Mail and Files Section - This section receives and processes for delivery a large volume of mail coming into the Division each day. The linear footage of open shelf files was increased about 30 percent to accommodate the growing number of active audit files for extramural grants. During the year this section received approximately 21,000 applications for research grants, 15,000 reprints, and 2,400 progress reports. Each of these documents required special processing and handling to insure delivery to the proper destination. In addition, this section maintains the current correspondence and record files for the Office of the Chief, DRG.

Travel Section - This section was increased in size to accommodate the additional workload reflecting the entire Division's growth and the resulting growth of review panels, committees, and study sections which are such an important part of the Division's operations. During the past year, this section received and processed over 7,800 travel vouchers involving an expenditure of close to $2 million for travel, per diem, and fees of Division personnel and consultants engaged in various review processes for the panels, committees, and study sections.

Serial No. DRS-1

DIVISION OF RESEARCH SERVICES

Summary of Program Activities
Calendar Year 1962

The Division of Research Services, which employs approximately 1300 persons with almost 200 individual occupational skills, provides scientific, technical, and engineering services to support and further the research programs of the National Institutes of Health. The Division is composed of an Office of the Chief and eight branches: Computation and Data Processing, Environmental Services, Instrument Engineering and Development, Laboratory Aids, Library, Medical Arts and Photography, Plant Engineering, and Research Facilities Planning.

DRS Programs -- 1962

The programs of the Division of Research Services can be divided into two broad classifications:

(1) Those in direct support of NIH research programs and (2) those related to the design, construction, alteration, maintenance, and environment of the NIH physical plant and facilities.

Programs in Direct Support of Research - These include the development, design and fabrication of special purpose instruments; the production of bacterial and tissue culture media; the preparation of sterile glassware; the production of genetically controlled small research animals; the quarantine and conditioning of larger research animals; animal surgery and recovery; animal disease control; photographic services, including motion pictures and slide films of surgical procedures, clinical photography of patient surgery and gross pathology and specimens, photomicrography and photomacrography; medical arts services, including medical illustration of surgical procedures and fabrication of plastic models to demonstrate clinical and pathological specimens; the development testing or control of special environments needed for research or clinical purposes; and computation and data processing services in support of individual bio-medical research projects.

Programs related to NIH Facilities and General Environment - These include engineering liaison in the design and construction of new NIH facilities; engineering work directed toward the development of improved facilities and equipment for bio-medical research; engineering and craft services required for the alteration and maintenance of the NIH plant and facilities; maintenance of the NIH grounds; and environmental services designed to maintain, protect and improve the health and well-being of NIH patients and employees and of laboratory animals used in NIH research programs.

As suggested by the above descriptions of DRS programs, the paramount objective of the Division is to provide a wide variety of scientific, technical and engineering services essential to NIH programs. Since virtually all of

these services are affected by changes in scope and direction of the institute programs, the Division makes a continuing effort to keep informed of institute plans and adjusts its organization, staffing, and functions accordingly.

For example, the increased need for germfree and specific pathogen-free animals in bio-medical research has led to the development of a program for the production of these animals, ultimately in substantial numbers, in our Laboratory Aids Branch.

Although the conduct of research is not a primary objective of DRS, it is essential that studies and investigations be carried out in the course of achieving program goals. Engineers, scientists, and technicians of the Division often work closely with institute scientists on important research undertakings. For example, the electronics engineer works as a member of a research team in the development of new instruments, the plastics expert assists the surgeon by the molding of heart valves, the mathematician programs research problems for application on the computer, and the veterinarian and geneticist provide healthy animals of various strains and types for research. This close working relationship between the DRS and Institute scientific and technical staffs has proved quite fruitful in producing results of considerable significance to bio-medical research. Typical of such results during 1962 were the development by an electronics engineer of the Instrument Engineering and Development Branch of a skin capacitance meter which measures the electrical capacitance of human skin, and shows promise as a screening tool for thyroid studies; the development, also by a Division electronics engineer, of a cartilage compressometer for the study of elastic properties of cartilage, which provides a new approach to research on the cause of diseases of the joints, such as osteoarthritis; and collaborative research between a veterinarian of the Laboratory Aids Branch and an investigator of the National Institute of Allergy and Infectious Diseases on a study of bovine ocular squamous carcinoma which led to the development of a method for reducing the recurrence of bovine ocular tumors.

Accomplishments

Construction

The following five major construction contracts were completed during 1962: New Surgical Wing, Building 10-A (exclusive of instrumentation); extension of the Refrigeration Plant, Building 11-C; Cage Washing Facilities, Building 14-F; Parking and Miscellaneous contracts for General Office Building #31; and the National Library of Medicine, Building 38.

Fourteen design projects totalling 66.5 million dollars were begun or continued during 1962. The major projects include: An NIMH/NINDB Building; a Cancer Research Facility; facilities for the NIH Animal Center; the NIH Office Building Extension; the NIH Master Utilities System Extension; the Gerontology Building; the Building 12 Extension; DBS Building 29-A; and the Puerto Rico Perinatal Laboratory.

Computer Program

Substantial progress was made in augmenting the programming and mathematical competence of the Division's central computer facilities. DRS staff members worked closely with a steering committee, representing NIH administration and Institute research programs, which devoted intensive effort to an analysis of the future orientation of computer applications at NIH. Of particular significance for the immediate future was the decision to acquire a second Honeywell 800 computer comparable with the one already in use and to proceed in the direction of acquiring substantially greater capacity as soon as possible. The new computer will become operational in early 1963.

Preventive Maintenance

During the year controlled preventive maintenance systems were put into effect by the Plant Engineering Branch as the final step in the over-all Controlled Maintenance Program that has been developed over the past several years. The new program is providing greater economy, better maintenance of facilities, and increased flexibility in meeting research program needs.

NIH Animal Center

Although the construction of permanent buildings at the NIH Animal Center is not scheduled to begin until the Spring of 1963, quarantine activities for large animals were carried out on a large scale at the Center during 1962 in existing farm buildings and other structures. For example, the average number of dogs under quarantine at the Center during the year was 228, compared with an average of 164 under quarantine at Bethesda. In addition, the use of facilities at the Center made it possible to increase the quarantine period for dogs from 2 to 4 weeks and to increase the issue of dogs for research programs from approximately 300 per month to 460 per month.

Staffing Changes

The following important staff changes took place during 1962:

1. Recruitment of a new Division Executive Officer to succeed the former Executive Officer who was made an Assistant Division Chief in late 1961.

2. Recruitment of a new Chief for the Environmental Services Branch.

3. Recruitment of a Supervisory Librarian.

4. Assignment of a full-time Management Analyst to the Division.

Problems

Alterations Backlog

During the past year, the Division experienced extreme difficulty in meeting the increased demand for plant alteration and maintenance services resulting from the growth of NIH physical facilities and the recent implementation of

a controlled preventive maintenance program. In the latter part of the year, limitations of funds resulted in an excessive backlog in the Plant Engineering Branch shops, causing undesirable delays in alterations vital to Institute research programs. This situation, coupled with the fact that the workload will continue to increase as new facilities now in design are completed on the reservation and at the NIH Animal Center, led to a decision in late 1962 to finance the Plant Engineering Branch shops activities under the Revolving Fund beginning in fiscal year 1964. It is doubtful, however, that this in itself will make it possible for the Division to respond effectively to the growing alterations workload.

The present and projected scope of the alterations program suggests that a really effective solution to the problem will lie in developing an equitable method of screening large jobs by the Institutes and Divisions to determine their necessity and degree of urgency and in devising an improved method of providing DRS with advance information of Institute program plans that will involve substantial alterations.

Recruitment of Mathematicians

The Division continues to have difficulty in recruiting qualified mathematicians for its Computation and Data Processing Branch. Part of the difficulty stems from our inability to compete with salaries offered by private industry, and from the fact that formidable hiring procedures established by regulations often lead to delays that discourage prospective employees and cause them to seek employment elsewhere. Perhaps an even more signficant contributing factor, however, is the lack of sufficient suitable space for our mathematicians. This aspect of the problem should be substantially alleviated when the Computation and Data Processing Branch occupies the top floor of Building 12.

NIH Computer Policy

The lack of NIH policies on the present and long-range application of computer technology at NIH continues to handicap the Division in planning to meet NIH needs for central computer services. Until such policies are developed and promulgated, it seems certain that a situation will persist in which neither the Institutes nor the central computer facility can plan effectively to meet NIH requirements in this area.

Medical Arts and Photography Branch

Serial Number	Title
3.1	Stereographic Surgical Camera
3.2	Injection Solution for Brain Radiography Technique

Laboratory Aids Branch

Serial Number	Title
4.1	Study of Bovine Ocular Squamous Carcinoma
4.2	Prosthetic Replacement of the Femoral Head
4.3	Testing of Castiplast 11, 17, and 327 (Resins of the Epoxy Type) In Tissue
4.4	Research in Animal Equipment and Facilities
4.5	Effect of Hydrochloric Acid and Chlorine Treatment Upon Pseudomonas Aeruginosa and Coliform Bacteria in Mouse Drinking Water
4.6	The Effect of Different Methods of Control and the Administration of Chemicals in the Drinking Water to Eliminate Coccidiosis from a Rabbit Colony
4.7	The Generation Time of Mast Cells of the Rat
4.8	Investigation of the Pathology of Cycad (Plant Family - Cycadaceae) Toxicity in Cattle
4.9	Chronic Murine Pneumonia of the Albino Rat

Laboratory Aids Branch (cont.)

Serial Number	Title
4.10	Mucoid Enteritis of Rabbits
4.11	Ringtail of Rats
4.12	Study of Causes of Death in Strain 13 and Strain 2 Inbred Guinea Pig Colonies
4.13	A Bacteriological Examination of Laboratory Animal Feed to Determine the Occurrence of Pathogens
4.14	The Effect of Piperazine Adipate in the Drinking Water for Three Days to Control Oxyurids in Female Mice and Their Litters
4.15	Papillary Cystic Adenocarcinoma of the Kidney of a Dog
4.16	A Study of Chronic Respiratory Disease in Rats
4.17	A Survey of Mycotic Diseases in Domestic Animals Submitted by the Communicable Disease Center, Kansas City, Kansas
4.18	Investigation of the Problem of Urinary Bladder Stones in Mice
4.19	Investigation of a Means for Clinical Diagnosis of Chronic Murine Pneumonia
4.20	Focal Necrosis of the Liver of Rabbits

Instrument Engineering and Development Branch

Serial Number	Title
8.1	Multi-Terminal Cortical Electrode for Chronic Implant
8.2	Experimental Analysis of the Motor Control Systems in Man

Instrument Engineering and Development Branch (cont.)

Serial Number	Title
8.3	Cartilage Compressometer
8.4	Neurosurgical Depth Electrode for Stimulation and Lesion-Making
8.5	Reversible Planar Brain Cooling
8.6	Automatic Pipetting Apparatus
8.7	Constant Current Cortical Stimulator

December 1962 Calendar Year 1962

PUBLIC HEALTH SERVICE - NATIONAL INSTITUTES OF HEALTH

DIVISION OF RESEARCH SERVICES

Summary of Branch Activities 1. DRS-2
Serial Number

2. PLANT ENGINEERING BRANCH 3. R. R. Holliday
Branch Chief

Objectives and Functions

In brief, it is the mission of the Plant Engineering Branch to provide the central services listed below for the National Institutes of Health. The Branch goal is to provide adequate services while utilizing manpower and material in the most economical manner.

Operation and Maintenance: These services consist of operating, maintaining and repairing NIH physical, mechanical, electrical, architectural and landscaping facilities as well as maintaining and repairing laboratory and research apparatus.

Engineering: These services consist of developing and preparing plans and specifications for alterations, repairs and extensions to the existing facilities, administering and inspecting construction work performed by private contractors, and providing professional engineering services as required.

Construction: These services consist of altering, installing and fabricating facilities and equipment for research programs. In this capacity the Branch furnishes mechanical, electrical and architectural craft services.

Summary of Branch Progress

The Branch workload continued to increase during the year in all departments.

Central Shops: The craft shop workload trend is determined by examining the number of work requests received, the relative size of the work requests and material used compared to previous periods.

The following table reports the number of work requests received within representative periods during the last two years.

Work Requests Received

Period	Total Number of Requests	Number of Major Requests
April, May, June '62	4583	1058
Sept., Oct., Nov. '61	2768	861
Mar., Apr., May '61	2435	647
Oct., Nov., Dec. '60	2590	427

More detailed analysis of the major work requests (jobs requiring the services of more than one shop, supervision, and/or estimated to require more than 16 manhours of craft time), indicated that not only are more requests being received but they are also larger in size.

Chart No. I reports the material used on work performed by the central craft shops both in terms of dollar value and number of line item issues.

The number of work requests received during April, May and June 1962 compared to March, April and May 1961 increased by 88 percent. The dollar value of materials used during the first nine (9) months of this year compared to the last nine (9) months of 1961 increased by about 45 percent.

To obtain some indication of overall shop efficiency, the material/labor ratio (that is, material cost per manhour of labor) for the first nine (9) months of the year was projected against the previous 18-month period. This is illustrated in Chart No. II. The trend (not considered an exact index) continues to be favorable.

In addition, trends reflected by the ratio of estimated manhours required over actual manhours expended for each job were favorable during the year. A cost performance report has been developed which reflects estimated over actual for material and labor (monthly and annually) in the various categories of work; however, plans to publish this data have been postponed until more consistent estimating can be done. Technical estimates are now being applied which are based on the judgment of an experienced craftsman. Plans for 1963 include the installation of engineered standards for estimating. This method of estimating, which utilizes standard data, will provide more consistent estimates and more meaningful data.

In the interest of comparing the adequacy of the service provided by the central craft shops, the periods of time required to complete jobs in various job size categories were determined and compared with previous periods. These results are reported by Chart No. III. In addition, the average shop backlog for the first eleven (11) months of the year was compared with previous periods. This information is reported by Chart No. IV.

While work procedures and methods have been improved, the increase in workload has more than offset these gains and resulted in a depreciation of the adequacy of the service. This trend is reflected by both Chart No. III and Chart No. IV.

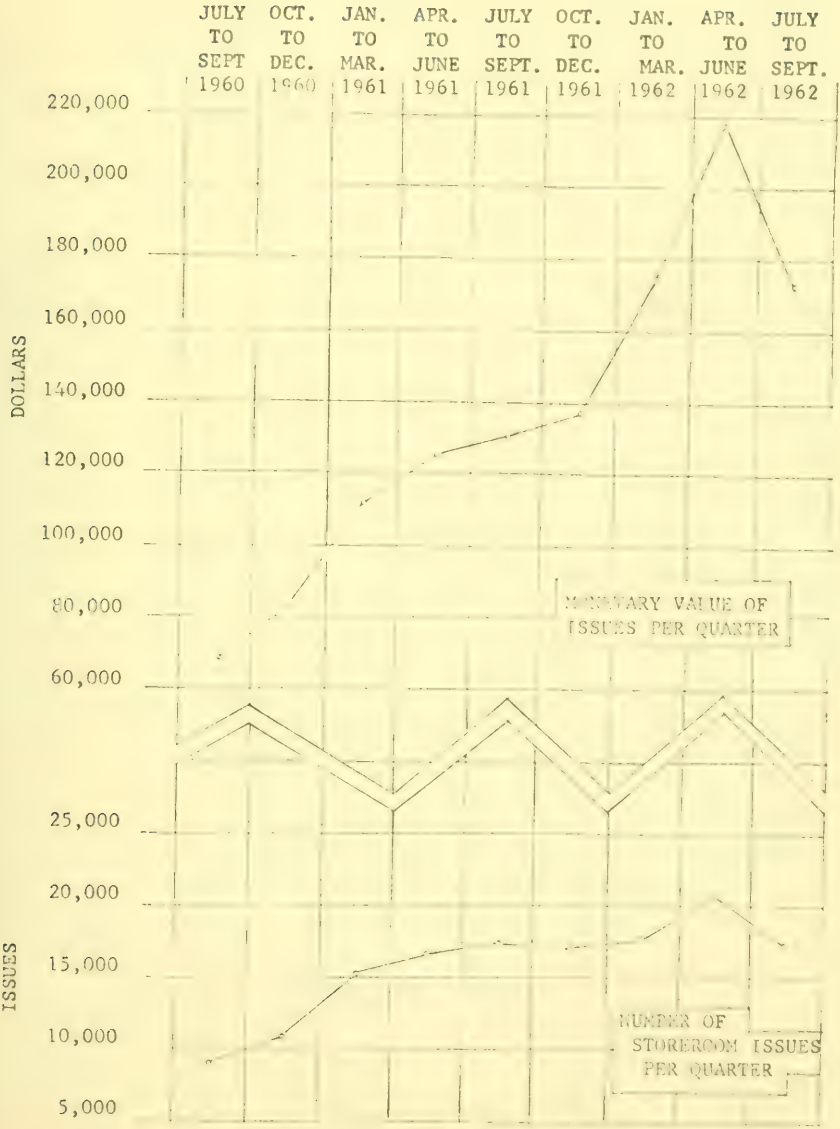

JULY TO SEPT 1960
OCT. TO DEC. 1960
JAN. TO MAR. 1961
APR. TO JUNE 1961
JULY TO SEPT. 1961
OCT. TO DEC. 1961
JAN. TO MAR. 1962
APR. TO JUNE 1962
JULY TO SEPT. 1962
220,000
200,000
180,000
160,000
140,000
120,000
100,000
80,000
60,000
DOLLARS
MONETARY VALUE OF ISSUES PER QUARTER
25,000
20,000
15,000
10,000
5,000
ISSUES
NUMBER OF STOREROOM ISSUES PER QUARTER

CHART NO. I

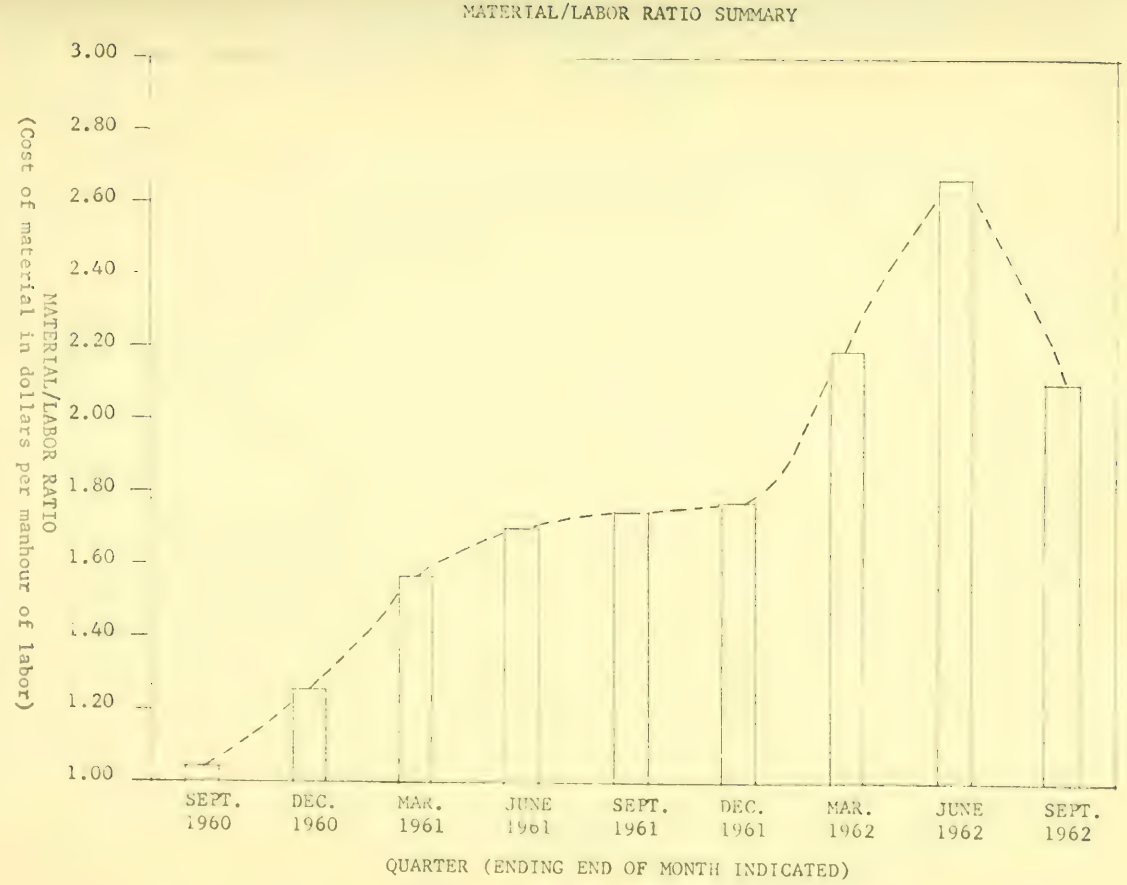
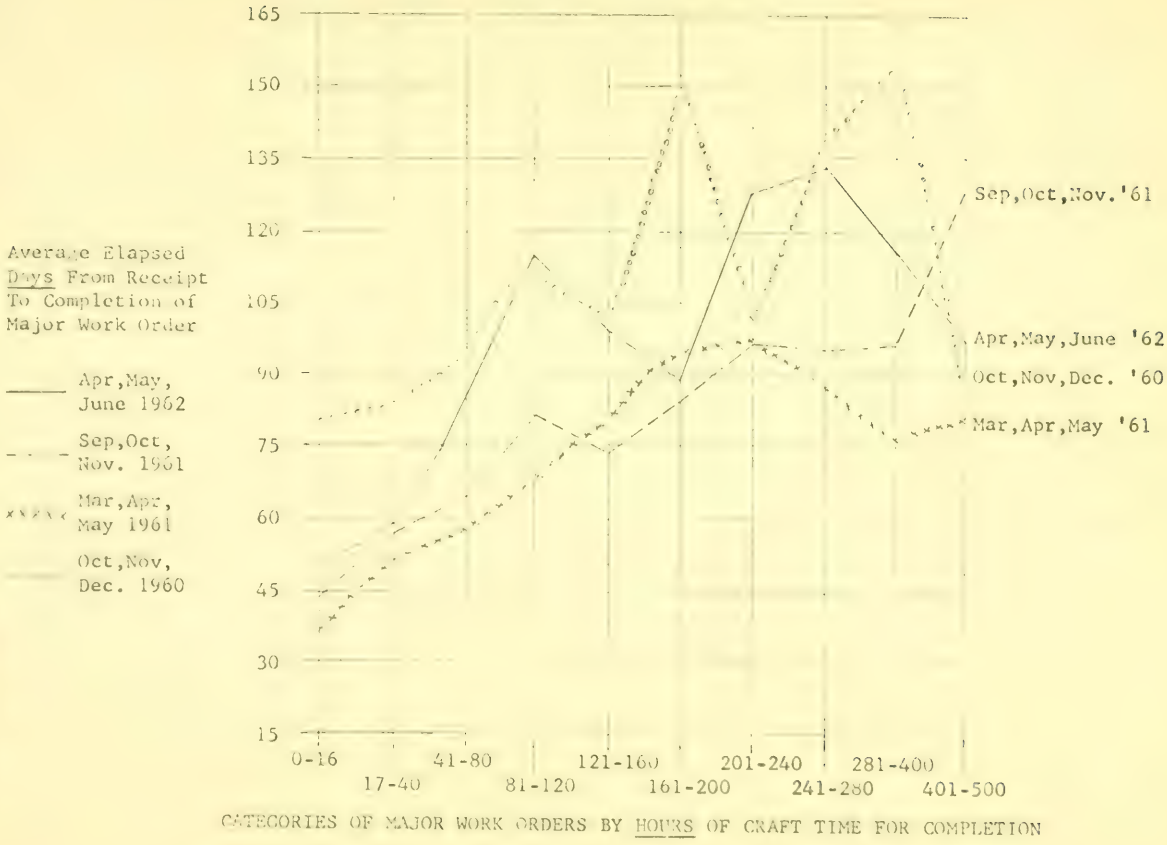

MATERIAL/LABOR RATIO SUMMARY
3.00
2.80
2.60
2.40
2.20
2.00
1.80
1.60
1.40
1.20
1.00
MATERIAL/LABOR RATIO
(Cost of material in dollars per manhour of labor)
SEPT. 1960
DEC. 1960
MAR. 1961
JUNE 1961
SEPT. 1961
DEC. 1961
MAR. 1962
JUNE 1962
SEPT. 1962
QUARTER (ENDING END OF MONTH INDICATED)

CHART NO. II

AVERAGE ELAPSED DAYS FROM RECEIPT TO COMPLETION OF MAJOR WORK ORDERS BY JOB SIZE CATEGORIES



SHOP WORK BACKLOG SUMMARY

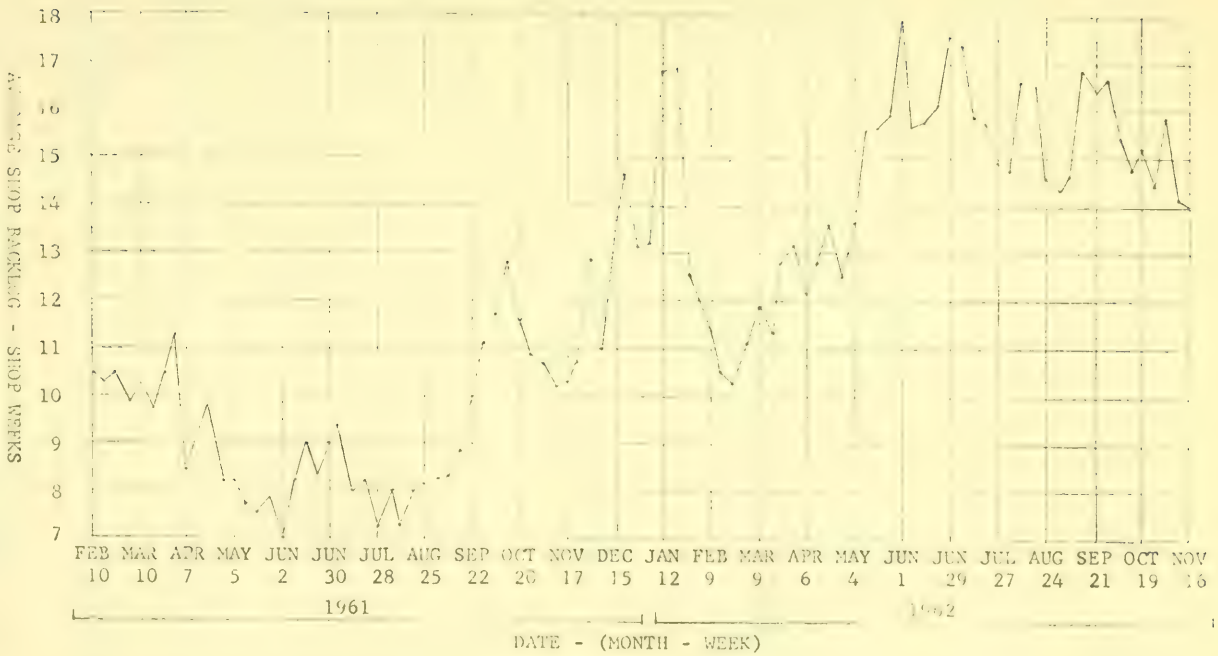


CHART IV

It is clear that the ratio between the average job completion time during calendar year 1961 are being reversed. The principal reason for this is that the rate of increase in work input has greatly exceeded the increase in numbers of personnel to perform work. No additional personnel were authorized in this area for fiscal year 1963.

Plant Operation and Maintenance: The plant operation and maintenance workload was increased during the year by the opening of buildings 11C, 31 and 38. These buildings represent an increase in gross floor space of over 17%, or about one-half million square feet.

With this increased load and the increase in activity at the NIH Animal Farm it became necessary to establish a fourth area maintenance unit within the Maintenance Engineering Section. This was done by abolishing one area maintenance unit which had become larger than desirable, and establishing two organizational groupings - one (the North Buildings Unit) assigned the responsibility for all buildings north of South Drive, except Building 10, and the other (the South Buildings Unit) assigned the responsibility for all buildings south of South Drive, except Building 11. Operational responsibilities for the NIH Animal Farm were assigned to the North Buildings Unit. About ten new employees were added to the units to handle the additional activities.

Contract Administration: The Branch provided the administrative and inspection services for 293 maintenance, alteration and improvement projects performed by private contractors. The total cost of these projects was about four million dollars.

These services exceeded the previous year's services by about 50% in terms of number of projects and by about 23% in terms of total cost.

In addition the Branch inspected and assisted the Regional Office, Public Buildings Service, with the administration of four projects handled through PBS for NIH. These projects cost about 3/4 million dollars.

Engineering Services: Construction contract drawings and specifications were prepared for over 200 projects awarded to private contractors during the first 11 months of the year. Some of the larger jobs are briefly identified below.

Building 1: The ground floor of this building is being remodeled to convert sub-standard space into a quality area for offices of the Personnel Management Branch. (Cost - $69,500)

Building 3: The first floor of this building was converted from office to laboratory use to serve program requirements of the National Heart Institute. (Cost - $85,000)

Building 10: A large part of the laboratory space on the 11th floor of this building was converted for new program activities of the National Institute of Allergy and Infectious Diseases. (Cost - $117,000)

Building 11: Four major improvement projects were developed for this building and placed under contract this year.

1. The brick refractory lining of the two incinerators was completely removed and rebuilt. (Cost - $23,375)

2. The air pre-heater tubes for the boilers were replaced. (Cost - $69,000)

3. A steam assisted oil atomizer burner was installed on one of the three boilers. (Cost - $25,500)

4. Defective planking was repaired, fan cylinders rebuilt, and a wood preservative treatment applied to the cooling towers of the Refrigeration Plant. (Cost - $25,500)

Building 12: A second Minneapolis-Honeywell computer system was installed adjacent to the existing one in this building. Portions of the work are under contract, and the remainder is being done with shop forces. (Cost - $62,000)

Building 14D: Two separate contracts are underway in this animal structure.

1. To convert space for a new monkey caging system. (Cost - $19,600)

2. To modify the west side of the building for the Polio and Measles Vaccine programs of the Division of Biologics Standards. This activity is to be transferred from Building 12. (Cost - $45,000)

Building 31: A basement area of this building was converted to house the NIH Printing Plant. (Cost - $54,000)

Many surveys and studies pertinent to work environment, operational safety, modifications for research equipment, and improvements to facilities and grounds were made during the year. The following are typical projects.

Emergency Electrical Facilities, Building 10: To assure a fully dependable emergency electrical system for patient operating facilities, safety equipment and similar essential electrical supply requirements, a study was conducted which permitted budgeting requirements to be established and funds requested.

Extension to Building 12: Site development studies were conducted to establish the relationship of this programmed extension to the existing structures surrounding Building 12, and to facilitate coordination with anticipated new buildings for this same area.

TV Inspection of Sanitary Sewers: A television camera study was made under contract of all the older sections of the sanitary sewer system to determine their soundness, and to provide data for the planning of any

needed repairs.

Child Study Center: A definitive program of requirements was prepared for a facility to replace Building T-4, scheduled to be demolished in the fall of 1963.

Roads and Entrances: A study was made to determine budget requirements for improvements to major entrance roads to the NIH reservation. Emphasis was given to requirements for improving the existing entrances and roads for external or visitor traffic, rather than internal or employee traffic.

An air conditioning supply and exhaust air filter selection guide was prepared, approved and distributed for the use of persons concerned with design of filters for NIH buildings. The guide provides a brief evaluation of filters, classifies them, and presents tables of low, medium and high efficiency filters. It also provides recommendations for selecting filters for various applications generally common to NIH facilities. It may be obtained from the Office of the Chief, Plant Engineering Branch.

Grounds:

Landscaping: Projects included in the Branch master planting plan scheduled for 1962 were completed. This work included foundation and screen planting for quarters buildings (Nos. 15A through 15G), screen plantings of azaleas, rhododendron and laurel along the NIH boundary at Glenwood, and extensive shrub plantings on slopes to reduce erosion and hand maintenance.

Research with a systemic (internal) insecticide requiring only two applications per year was promising. Its use will be expanded in 1963 to provide better control at less cost.

Erosion Control: The creek in the southeast corner of the reservation was straightened and graded. Sod was established on the creek slopes to improve appearance and reduce hand maintenance.

Storm water flooding near Cedar Lane and West Drive and near Building 32A was eliminated with the completion of adequate drainage systems.

Lawns: All turf areas suffered severely from drought during the summer. About 30% of the outlying turf area was killed. After fall fertilizing, aerifying and reseeding, and several showers in September, many damaged turf areas began to recover. However, extensive spring renovation will be necessary.

Large trees: Drought damage to trees is impossible to assess at this time. Attempts to minimize damage during the summer drought included severe pruning of certain varieties of trees to reduce root load, deep feeding to increase vitality, and deep watering to stop dessication.

Personnel: As of November 20, 1962, the Branch employed 552 employees, an increase of 53 (roughly 10 percent) over January 1, 1962. Five hundred and thirty-six (536) were permanent employees and 16 temporary. This year, for the first time, the Branch began supporting its permanent staff with temporary employees. This was done in order to provide flexibility for the varying craft workload, for budgetary control, and to tap a heretofore untouched labor pool.

During the past year the Maintenance Engineering Section was brought to the full personnel strength necessary to provide around-the-clock operational services for buildings completed as a part of the major construction program of NIH.

Training: The Branch supported some 5,523 classroom hours (691 man-days) of instruction during the year as compared to 5,576 the previous year. Of this, 176 manhours were in the field of management and supervision and the remainder in professional or technical subjects. The preponderance of the training received by Branch employees was presented within the Branch itself. Only 260 manhours of training was taken in other government agencies, and only 1160 in non-government facilities.

The North Buildings Unit, the South Buildings Unit, the Elevator Unit, and the Clinical Center Unit of the Maintenance Engineering Section continued formal programs of instruction in maintenance and operation of plant equipment.

Awards: The drive launched in previous years to stimulate employee suggestions has had excellent results. The Branch is now receiving an average of two or three suggestions a week. While it is difficult to assess the value of an awards program by the sheer number of suggestions submitted, it does indicate that employees are becoming alert to better ways of doing the job. During the past year twelve (12) awards were given to employees for suggestions and/or work performance. Since the present rate of submission dates back only a few months, the majority of the suggestions submitted are in the process of being evaluated, and the full worth of the program will not be felt until next year.

PUBLIC HEALTH SERVICE - NATIONAL INSTITUTES OF HEALTH

DIVISION OF RESEARCH SERVICES

Summary of Branch Activities

1. DRS-3
Serial Number

2. MEDICAL ARTS AND PHOTOGRAPHY BRANCH
Branch

3. Malcolm S. Ferguson
Branch Chief

Objectives

The primary objective of the Medical Arts and Photography Branch is to provide techniques, equipment and services to assist laboratory and clinical investigators of NIH in the visual recording of biomedical phenomena and information and the dissemination of new knowledge to research and practitioner groups, both here and abroad.

Programs

The Branch, through its medical arts services, produces clinical drawings, general illustrations, exhibits, charts and graphs, varityping, publications design, silk screening, moulages, museum mountings and specialized plastics materials. Its photographic activities include a range of services: still photography, both in black and white and color, with subsequent production of prints and slides; and motion picture coverage of subjects where movement and action are significant. Art and photographic competencies are mobilized and coordinated for the production of animation sequences to be incorporated in motion pictures. The Branch engages in investigations with a view to developing new techniques for the documentation of research observations through art and photography, and in the use of the camera and illustration as research tools. In addition, fine and applied arts consultation is provided for decor and furnishings of administrative offices, conference rooms, and other special areas, both at NIH and in other segments of the Public Health Service.

Summary of Progress

Steps were taken during 1962 to promote a closer coordination of the activities of all Branch components to obtain greater efficiency of operation. Reorganization of the Photography Section has resulted in improved working conditions and higher production. A reference service for the research staff of the Institutes, as well as Branch personnel, was initiated in the form of an information file on visual documentation techniques, experts in visual communications, and titles of motion pictures. Three motion pictures were completed, with valuable experience being gained during their production. Animation sequences for films were produced for the first time. Requests for art services increased twenty percent and requests for photographic services eight percent over 1961.

Non research-related requests for service were curtailed and investigators encouraged to make use of private contractors for photographic printing. Art and photographic services have been speeded up through space renovations, acquisition of new equipment, and emphasis on automation.

Accomplishments

Coordination of Visual Communication Services. The Medical Arts and Photography Sections gradually evolved and grew over several years and, up to the present, have operated as relatively autonomous administrative units. Now that they are joined as the sole components of a separate Branch, it is obvious that improved coordination of effort in certain areas is necessary to achieve greater efficiency and an increase in output of services relative to the costs involved. An organization and management study of all Branch activities was initiated late in 1962, and it is expected that from this will come guidelines for future administrative and operational changes. Already the Photography Section has been reorganized into three units, the esponsibilities of supervisors more clearly defined, and internal communications improved. A similar realignment of the Medical Arts Section is underway to simplify its structure. As improved management policies are developed and effected, and as a more cohesive visual communications program is evolved, the Branch Office will come to exert a greater influence on overall sectional activities.

Changes and Improvements in Services. Due to the great expansion of NIH research programs in recent years, the demand for art and photographic services has increased to the extent that presently it is impossible to satisfy all demands for service. While there have been substantial staff increases in recent years, other means of meeting the needs of the investigator have also been emphasized. The use of contractual services by NIH personnel for obtaining certain types of exhibit construction, the large-scale printing of photographs, drafting, etc., has been encouraged by the Branch as a means of alleviating its workload. New photographic processing equipment of higher capacity has been installed, with emphasis on automation. The photographic darkrooms have been rearranged for greater efficiency.

The management study previously mentioned has indicated a need for spatial rearrangements in the photographic area to facilitate operations and partially relieve serious crowding conditions that have interferred with performance of photographers and laboratory personnel. The quality of photographic services can be expected to rise as a result of these improvements and the greater emphasis that will be placed on individual performance.

Medical Arts Services. During 1962 more work of a complex nature was performed and overall production increased about twenty percent above the 1961 level. In all there were approximately 3,000 requests for service and 12,000 pieces of art were produced. The greater volume of service rendered was made possible through a modest increase in staff, the renovation of working space, and improvements in the handling of individual parts of complex projects.

Eighteen major exhibits were produced for NIH in 1962, and fifteen older exhibits were renovated and updated. These were shipped to 114 meetings in various parts of the United States and Canada, and in Europe - specifically to Portugal and Germany.

Clinical illustrating has continued to be in demand, with ophthalmological drawings from both animal and human subjects being emphasized. Three dimensional models were produced, including two wire sculptures, one of which illustrates the vascular system of the chick embryo.

A wide variety of general illustrating was performed. Besides supplementing the design of exhibits and publications, production involved subjects such as sequences and titles for animated films, slide series for use in lectures, flip charts, artwork for television, and a number of specialized projects. Typical of the latter was the development of methods whereby a number of charts on the international support of research by NIH could be simultaneously produced in color as 20" x 30" enlargements and in black and white as 8" x 10" reproductions of the original artwork. The latter technique can be applied to production of most of the administrative charts required at NIH, with material reduction in cost and time.

The design and preparation of scientific publications continues to expand, with many items requiring a special approach. For instance, in a publication dealing with mental problems of the aged it was necessary that the booklet be informative but not unduly depressing.

In the area of statistical drafting, the heavy workload has led to a search for approaches that will improve both efficiency and accuracy of the day-to-day operations. Drafting personnel are now being called on to produce a larger number of cartographic and technical illustrations, such as representations of molecular models and operating room and laboratory apparatus.

In the museum preparations area, a number of processes are being investigated. These pertain to studies of preservatives for biological specimens that will retain tissue color, sealants for museum jars, and resins for embedding tissues that have suitable hardening properties.

Fine Arts Consultative Services. This function is performed for the Branch by a Fine and Applied Arts Specialist who was formerly Chief of the Medical Arts Section. There were significant accomplishments during 1962, among the more important of which were: detailed plans, scale drawings, and color schemes for renovations of administrative offices at NIH, in other Bureaus of the Public Health Service, at St. Elizabeths Hospital, and the refurbishing of a Congressional Committee Room; and the planning of exhibits for the 75th anniversary celebration of research on infectious diseases by the Public Health Service. This service is available to all NIH organizational units, and to other components of PHS, and the Department.

Still Photographic Services. Two units of the Photography Section are devoted entirely to still photographic processes - both black and white and color. The Section was continually swamped with work, in spite of efforts at streamlining of procedures, greater emphasis on automation, improved spatial arrangements, the trimming of requests for photographic prints where the number asked for appeared excessive, diversion of some requests by encouraging Institute personnel to use the outside contract mechanism, and the elimination of certain non-research related requests. In 1962, there were

13,000 requests for service, with an average of [illegible] per day. The number of black and white prints produced was 133,113, a decrease of almost 30,000 from the 1961 level. Likewise, black and white slides decreased about 2,000 below the 50,653 produced in 1961. Both of these decreases reflect the use of contract photo finishing services by Institute personnel and greater emphasis by the Photography Section on the policy of accepting only research related requests.

During the year, photographic services deviated from the normal routine in three principal areas: the recording of gel diffusion tests for antigen-antibody reactions; the reproduction of x-rays and sonograms; and the production of 2" x 2" slides, both originals and duplicates of clinical, laboratory, and technological subjects (12,694 black and white).

Color film processing is increasing due to a greater demand from the research laboratories. Coincident with this, the requests for color prints are mounting. At present, however, the facilities for such printing are not adequate and this service is performed by the outside contractor.

Clinical and laboratory photography services covered a wide range of subjects: human patients, experimental animals, gross specimens, immunological tests, starch gels, tissue sections, apparatus, etc. Photomicrographs of higher quality were produced in greater number due to the acquisition of new equipment with a built-in light source and sensitive exposure controls. This whole area of service requires a close and harmonious relationship between photographers and the clinical and laboratory investigators.

Informational photography accounted for 915 requests in 1962, ranging from simple setups and coverage of scientific meetings to involved assignments requiring extensive travel. For instance, photographs of various field and laboratory activities were obtained for use in exhibits; an extensive documentation was made of ecological factors related to the field transmission of polyoma virus; and activities in clinical research centers in various parts of the country were photographed.

Motion Picture Services. Requests for motion picture documentation of clinical, laboratory and other activities increased over 1961. Nearly 35,000 feet of film were exposed and of this amount 28,000 feet were edited into complete units of varying length. Sound was also recorded in the amount of 4,800 feet. In all, 23 different projects were documented, including such subjects as heart surgery; heart valve studies; oral pharyngeal and vocal chord studies; behavior of rats in response to various stimuli; drug-induced behavior patterns in animals; eye movement studies; and muscles controlling movements of bones in the middle ear. Several sequences on tests for glaucoma were photographed for use in a film on blindness produced by the World Health Organization.

Three edited films complete with sound were produced during the year. These involved both medical arts and photographic personnel, since animated sequences were included. This 9 minute film on heart research is receiving world-wide distribution through the U. S. Information Agency. A second film depicted nerve pathways in the brain, and the third dealt with the function of photo-receptors in the retina of the squid.

The Branch now has had sufficient experience in motion picture production to enable it to engage in this work more actively. It is anticipated that during 1963 the production of several films on research-related subjects will be undertaken. Facilities for this growing program have been greatly improved with the acquisition of a new sound tape recorder and professional animation equipment.

Program Development

Resource File. A visual arts and communication reference file has been initiated in the Branch office. This collection will contain abstracts of papers on photographic and illustrational techniques and their use in scientific research or in the documentation and dissemination of technical information. In addition, there will be an extensive file of information on individuals active in the fields of photography, cinematography, television and art, as well as titles of motion pictures produced here and abroad. It is anticipated that these reference materials will be of value not only to Branch personnel but also to the research, communications, and administrative staffs of the Institutes. The file will be developed in conjunction with procedures being devised for the identification and reclassification of the Branch's extensive collection of photographic negatives, transparencies, and pieces of artwork.

Scientific and Technical Communications. During the summer, Branch personnel prepared an extensive report on Division of Research Services activities in the biomedical communications area for submission to the Surgeon General. This and reports from the Institutes and other Divisions of NIH, as well as from other components of the Public Health Service, served as working documents for a conference in November to consider general recommendations leading to a dynamic PHS-wide program of scientific communications to investigators, practitioners, and the general public. The Medical Arts and Photography Branch is in a key position to provide consultation and leadership in certain aspects of the new information dissemination program at NIH which will revolve around the offices of the proposed scientific and technical communications officers of the Institutes and Divisions.

Staff Training. During the year key personnel in the Branch went to professional meetings and attended courses of instruction in communications techniques to become acquainted with new approaches and equipment, and to discuss problems and procedures with colleagues from other institutions.

Methodology Research. In both the art and photographic components of the Branch a limited amount of investigation is directed toward the development of new techniques, improved equipment, and the modification of materials for specific needs. Work of this nature on fixatives and embedding materials has been mentioned previously. Personnel in the Photography Section have engaged in such projects as design of equipment for photographing agar plates as a standardized procedure; development of procedures for photographing colloidal phenomena; an improved method for producing 35 mm cardboard mounted slides, both from black and white negatives and color transparencies; studies of lens specifications for enlargers and cameras; application of photogrammetric methods to the design of equipment for photographing three-dimensional models; and the development of a prototype stereo camera for use in neuro-surgery.

Serial No. 3.1
1. Medical Arts & Photography Branch
2. Photography Section
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A

Project Title: STEREOGRAPHIC SURGICAL CAMERA

Investigators: Vernon E. Taylor, Photography Section
Edward J. Laskowski, Jr., MD., NINDB/SN
Gomer T. McNeil, President, Photogrammetry, Inc.

Man Years (Calendar Year 1962):
Total: .1
Professional: .05
Other: .05

Project Description:

Objective: To devise a simple, inexpensive camera using stereo techniques to record physical changes before, during, and after neurosurgery to indicate depth of incision, volume of area removed, and color differentials of surface and subsurface tissue.

Methods Employed: By investigation of current photogrammetric techniques, testing a variety of optical systems, and finally choosing and re-designing standard equipment applicable to the visual recording of neurosurgical procedures.

Investigative Procedures: By coupling and modifying existing Japanese cameras and optical systems a unit with a simplified field location and focusing system was built that is capable of producing slightly hyper stereo images. A synchronous electronic flash is coupled with the system. The equipment is prelocked so that it can be easily handled by surgical personnel with a minimum of familiarization. The system uses standard 120 roll color or black and white film affording an image size useable for direct visual study, contact and enlarged prints, and color transparencies.

Part A (Cont'd)

Significance: The photographs made with this equipment contain information contributing to a more complete visualization for study and review of neurosurgical or other procedures, for the making of accurate 3-dimensional models, and for publication. The photos may be viewed or published either singly or as stereo pairs.

The same equipment may be used for progress studies in orthodontics.

Proposed Course of Project: Continuation

Part B included Yes _____ No X

Serial No. 3.2
1. Medical Arts & Photography Branch
2. Medical Arts Section
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A

Project Title: INJECTION SOLUTION FOR BRAIN RADIOGRAPHY TECHNIQUE

Principal Investigator: Mr. Philip Joram

Other Investigators: None

Cooperating Units: Diagnostic X-ray Department, Clinical Center

Man Years (Calendar year 1962):
Total: .10
Professional: .10
Other:

Project Description:

Objective: A radiopaque injection solution to permit detailed X-ray study of all blood vessels in the head and brain.

Methods Employed: A previously published technique was modified. Various ratios of acetone solvent to liquid lead matrix were made to find a solution that would penetrate the smallest as well as the major blood vessels, and yet permit detailed radiographs of these vessels. This solution was then tested with different ratios of vinyl acetate to give a final mixture with a certain degree of rigidity on solidifying.

Significance: The new solution provided for ease of injection and sufficient density to permit radiography of all vessels in the head and brain.

Proposed Course of Project: Completed

Part B included Yes _____ No X

PUBLIC HEALTH SERVICE - NATIONAL INSTITUTES OF HEALTH

DIVISION OF RESEARCH SERVICES

Summary of Branch Activities

1. DRS - 4
Serial Number

2. LABORATORY AIDS BRANCH

3. Dr. Preston Holden
Branch Chief

SUMMARY

The dramatic growth of NIH is mirrored in the ever increasing quantities of research animals, media and glassware furnished by Laboratory Aids Branch. As is true in most operations, however, workload measurements alone tell only a fraction of the story. They give no indication of the long range planning, coordinating, problem solving, etc., which accompanied or preceded these services.

During 1962, plans for buildings to be constructed under Phase I at the NIH Animal Center were completed. Renovation and construction projects on animal facilities at Bethesda were either completed or are nearing completion. Physical plant expansion will provide permanent housing for farm animals, increased quarantine and holding space for dogs and cats, primate research modules, and additional space for germfree, specific pathogen-free and conventional animal breeding colonies.

Pilot studies under way during the year included breeding of cats, germfree and specific pathogen-free animals. These have been issued in limited numbers for evaluation by interested scientists. Small scale tissue culture cell production, used mainly in quality control procedures, provided a means by which potential for future large scale production could be measured.

DRS, Laboratory Aids Branch, cont'd:

Developmental studies in the fields of animal equipment, methods of animal care, and maintenance of rooms and ancillary facilities were initiated in cooperation with the Research Facilities Planning Branch.

The multi-disciplinary approach to studies on diseases of laboratory animals, adopted by Comparative Pathology scientists, is proving successful.

Accomplishments

Adhering to the principle that sophisticated research can be performed only under adequately controlled conditions, greater effort was made to provide high quality animals and other services.

During 1962, Branch scientists cooperated with several NIH investigators in developing strains of animals with specialized characteristics. For example, colonies of rabbits with specific gamma globulin types were developed for NIAID.

The addition of staff members well trained in microbiology and clinical chemistry greatly increased the overall effectiveness of the Comparative Pathology Section in providing diagnostic and disease control service for the NIH animal production colonies. The merging of these disciplines with the pathology program made possible much more thorough studies of many of the long standing problem diseases of laboratory animals. In a relatively short time, these studies have produced new information on the pathogenesis of poorly understood conditions such as pregnancy toxemia of guinea pigs and mucoid enteritis of rabbits. The characterization of pregnancy toxemia has progressed rapidly and led to the development of means of reproducing the condition experimentally. At this time, recommended methods of prevention of the condition appear to be effective in the Strain 13 and Strain 2 inbred guinea pig colonies. A previously undescribed bacterium with fastidious cultural characteristics has been found in large numbers in the intestines of rabbits with mucoid enteritis. Thus far, considerable difficulty has been encountered in attempts to isolate the organism in pure culture and to demonstrate a direct causal relationship between presence of the organism and the disease process. However, this work continues and eventual success is expected.

An outbreak of rapidly fatal enterotoxemia was detected in the rabbit colony for the second consecutive year. Unlike last year, the disease was confined to one room and did not cause heavy losses. Attempts to further characterize the condition were thwarted by the short duration of the outbreak. However, plans have been formulated for thorough studies when and if future outbreaks occur.

These and other studies have been greatly facilitated by the adoption in the Comparative Pathology Section of closed module animal caging techniques. The use of these Horsfall type units has permitted the introduction of numerous infectious agents into the Section's one animal room without apparent spread of agents from one cage to another.

The jaundice gene presently found only in the JU/CN strain of rats was introduced into the Buffalo strain of rats for the National Cancer Institute. This was done by a cross followed by a series of backcrosses with alternate brother x sister matings.

Through studies performed in cooperation with the Environmental Services Branch, a successful technique was developed for the sterilization and introduction of supplies into plastic isolator units.

High mortality in cesarean-derived Sprague-Dawley rats presented one of the most perplexing problems to be solved in this area. Several months were spent trying to establish this strain in the germfree units. Germfree rats (LOBUND strain) were obtained from NIAMD for use as foster parents. However, the longest any cesarean-derived Sprague-Dawley pups lived on a germfree LOBUND mother was fourteen days. Small and dehydrated, the young died of starvation. Many times the mother would raise one or two of her own, but not the strange young. Eventually, the Sprague-Dawley rats were raised by a family of germfree Fischer rats obtained from NIAID. The LOBUND rats have since been issued to provide more room for the now rapidly expanding Sprague-Dawley colony.

Some difficulty was also experienced in establishing the inbred BALB/c mouse in germfree isolators. The problem here was obtaining females at full term. Once this difficulty was overcome, it took only a few attempts at foster nursing to establish a family of germfree BALB/c mice. Expansion of this colony is now in progress.

Six Reyniers 500 Series isolators were received in August. Two have been set up for rats, and a third is in the process of being set up.

Specific Pathogen-free animals are also housed in Building 10. Eighty-eight SPF-NIH mice were moved from the isolators to Building 14E for use as foster parents of a new colony of General Purpose mice now in Building 14F. At the present time, the same procedure has been instituted on a smaller scale with Sprague-Dawley rats.

Thus far, this report has dealt principally with animals; their sources, facilities, and the peripheral skills which are necessary to the success of a program of this magnitude. At this point it is logical to examine the other aspects of the Branch program, namely, media production and glassware preparation.

In both of these areas, the rising trend in production experienced over the past several years continues at a significant rate. Production figures projected to the end of the year indicate an approximate 18.2% increase over 1961 in numbers of requisitions filled in the Media Unit and a 13% increase in pieces of glassware issued from the Glassware Unit.

A new media request form which replaces four forms previously used in the Media Unit, has greatly facilitated work in the Unit. In addition, the new form provides requestors with a listing of ingredients in each order, thereby eliminating many phone calls for this type of information.

A basic catalog of tissue culture media and solutions, as prepared in the Media Unit, was completed and distributed to media users. This catalog provides the individual requestor with exact information on the content of any given lot of media. Periodic additions to this catalog will be made as the need arises.

Major modifications were made on three of the six autoclaves in the Media Unit to alleviate a recurring problem of gasket replacement. The three remaining autoclaves will be scheduled for similar modification as time and money permit.

A second large autoclave has been installed in the Glassware Preparation Unit. Use of this equipment will provide additional safeguards to employee health.

Cooperative studies were carried out with the Environmental Services Branch to determine the overall level of contamination present throughout the Media Unit. Plates exposed to determine an initial contamination level, before any general cleanup of the areas was attempted, indicated a fairly heavy contamination, predominately of the Neurospora type. After this initial sampling, several steps were taken to improve conditions in the sterile work areas. These included removal of unnecessary equipment from sterile areas, use of disposable caps and masks by personnel, washing down work surfaces immediately before use with a suitable disinfectant, and working directly over disinfectant-soaked towels. It was gratifying to note that these few steps achieved a 25-50% reduction in the level of contamination in these areas. Since it has been fairly well established that most of the contamination problem is due to excessive traffic through the Media Unit, steps to more effectively control such traffic will be taken.

Stainless steel sorting tables and shelves, installed in the dirty glassware sorting area, have greatly improved the overall efficiency and appearance of this area.

A surplus automatic tumbler type clothes washer has been successfully used to wash such things as screw caps, stainless steel tube closures and rubber stoppers. Specifications were submitted for two new deionizers which will be ordered by Plant Engineering Branch to replace the present, inadequate, machines. The new deionizers will have a higher capacity, provide more efficient filtration of the water and save a great deal of the time and effort presently required for regeneration of the old machines.

The final working drawings for the renovation of space for tissue culture cell production were completed by the Engineering and Design Section, PEB.

During the year several different types of tissue culture cells were obtained and different methods of freezing them were tried, with the result that a frozen tissue culture cell bank has been started. Limited quantities of tissue culture cells were issued to selected users in several Institutes on a weekly basis for their evaluation. All of the users reported the cells were completely satisfactory.

After critical testing in cooperation with the Clinical Center Clinical Pathology Section, commercial rabbit blood has been accepted for use in bacteriological media. This development has been of real benefit to the Media Unit. By freeing two men of some eight man-hours per week caring for and bleeding rabbits, it has been possible to increase significantly the plate output by these men.

Program Developments

In cooperation with RFPB, a major program on the development of animal caging and housing systems has been initiated. Three basic principles will be kept in mind as the new systems are developed: (1) The system should require a minimum amount of labor for proper operation; (2) the animals' environmental requirements must be met; (3) the system should provide a barrier against entry or exit of unwanted microorganisms. Insofar as possible, all new design concepts will be tested with prototypes. As a part of this program, research on optimum environmental conditions for laboratory animals will be undertaken.

While exposure to disease conditions in the NIH colonies is rigidly controlled, this is not possible in the Animal Hospital where animals are received from outside sources. As a result, the disparity between the quality of dogs and cats available for medical research and the quality demanded by medical researchers continues. The average quality of animals available from commercial sources is continuing to deteriorate because many of them are shipped by truck for several hundred miles and held for many days in compounds before delivery to NIH.

With the addition of supplemental quarantine facilities at the NIH Animal Center, more dogs have been available of a quality suitable for long-term experiments. The animals which are available for non-survival experiments are often less than satisfactory, however, and many investigators are ordering sturdier animals for use in these experiments, thus further increasing the demand for quality animals from the cat and dog quarantine.

The purchase price of monkeys used in medical research has been reduced again this year. Also, during July, August and September, the quality of these animals was improved by rapid jet transport from India to the United States. During the last quarter, however, disease outbreaks in newly arrived monkeys increased. This may reflect changes in holding practices in India or exposure to colder weather enroute, or both.

A gamma globulin type appearing only in the Flemish strain of rabbit is being introduced into the New Zealand White strain by a cross followed by a series of backcrosses. Three or four small colonies homozygous for other gamma globulin types are under development in the Flemish rabbit colony. This work is being conducted in collaboration with the Laboratory of Immunology, NIAID.

Cage cleaning always produces a certain amount of dust and the caretaker invariably contaminates his hands and clothes during the cleaning process. Therefore, a program of requirements for a vacuum cleaning system in the cagewashing area has been developed. Such a vacuum system will increase the efficiency of cage cleaning and enable a larger number of cages to be cleaned in the cagewashing area.

The health and reproductive efficiency of the rabbit colony has improved markedly in the past two years. It is felt that this improvement is due to more strict attention to proper caretaking and animal husbandry procedures. New breeders are now selected on the basis of physical conformation and production records of their parents. Poor breeders are culled from the colony. Close surveillance permits detection of sick animals and their prompt elimination. Caretaking procedures are carried

out according to standard operating procedures. A larger percentage of successful matings has resulted from increasing the time that some females are with the male from a few minutes to overnight. As a result of these improvements, the shortages of past years have been overcome and virtually all requests for rabbits can now be filled by our Animal Production Section.

During 1962 almost all mouse production was converted to a system employing monogamous breeding pairs. At the same time, frequency of cage cleaning was changed from once to twice a week. Cages are now washed and sterilized at each cleaning. In addition, all mice are handled with disinfected forceps. This system has reduced the incidence of diarrhea in suckling mice. It also makes possible the production of more mice within the same space. The most gratifying aspect of these husbandry procedures is the apparent increase in the quality of the mice produced. They grow well, have smooth hair coats, in general look healthy, and have a low cull rate.

A most significant program development this past year has been dissolution of the old general purpose mouse colony in Building 12 and the establishment of a new cesarean-derived general purpose (GP) mouse colony in Building 14F. The "old" general purpose colony was maintained in sub-standard physical facilities in Building 12. Although reasonably healthy, these animals harbored a number of parasites and microorganisms considered detrimental to many research projects and to the efficiency of production. It had been known for some time that the colony was to be moved from Building 12 to Building 14F when renovations to the latter had been completed. To avoid moving our poorest quality mice into our best new animal quarters, it was decided to establish a new cesarean-derived general purpose mouse colony. In doing so, great care was taken to assure genetic continuity between the "old" colony and the "new."

Several major steps were taken in establishing the new colony. Cesarean sections were performed on a carefully randomized and selected group of 166 pregnant females from the "old" colony. This large number of csections was necessary to assure, as nearly as possible, continuance of the genetic pool. The cesarean-derived young were foster nursed on ex-germfree

lactating females. Altogether, a total of 1,206 foster nursed mice have gone into the foundation breeding stock of the "new" colony.

The foster mothers used in developing the new colony were held in plastic germfree isolators. Initially germfree, they were deliberately contaminated with four artificially cultivated bacteria; namely, two species of Lactobacilli, an Enterococcus, and a slow lactose fermenting gram negative rod. This deliberate contamination with a known microflora was done to increase resistance to intestinal infection with unwanted microorganisms such as Salmonellae, Pseudomonas aeruginosa and certain endotoxin producing strains of E. coli.

The "new" colony will be maintained under rigid sanitary conditions. All feed, bedding and equipment entering the colony rooms will first be sterilized or sanitized. Personnel will observe work rules designed to increase the odds against contamination of the animals with unwanted microorganisms. For example, the animals will be handled only with instruments or gloved hands. This rule will apply also to water bottles, feed, bedding and other objects with which the animals have intimate contact.

The animal production specialists are not trusting blindly that improved "work rules" and other refinements in technique will successfully exclude unwanted infections from the SPF colonies. Bacteriological tests are made weekly on fecal specimens to ascertain the predominant bacterial species in the intestinal tracts of these animals. Arrangements are being made for appropriate testing for the presence of viruses. Thus, information will be available on the presence or absence of specific infections in the colony.

Considerable experience has been gained from the maintenance of germfree animals over the past year. Production of NIH mice on a limited scale was possible through the loan of both equipment and space in NIDR laboratories. This provided experience in (1) training personnel, (2) production in large isolators, (3) issuing animals to germfree laboratories in other buildings, and (4) keeping records.

Space occupied in Building 10 was used primarily for the development of standard techniques and equipment modifications.

Nucleus colonies will also be formed in these facilities prior to transferring Germfree Production to permanent quarters in Building 14G.

After more than a year of routine issuing of the Kimler-Wheaton bottles by the Media Unit, it is apparent that their unique design and higher quality have resulted in widespread acceptance. However, the rate of return has been insufficient to allow for the maintenance of an adequate stock of these bottles. Supply Management Branch was contacted and requested to stock these items so as to make them readily available to all users. They have agreed to do so immediately. It is hoped that this will alleviate the problem of inadequate stock.

Problems

Monkey Supply

Two factors may affect the supply of primates during the coming year. First, the colony will be moved to more compact quarters where there will be no space available for expansion and very little space for the holding of unusual species of monkeys. The second factor is the attack of the Chinese Army on India, especially in the Ladakh area of Kashmir. This area of conflict is within 250 miles of the area where much of our monkey supply is trapped. Should the Chinese invade further, it is possible that we will have to seek other sources of, or substitutes for, Macaca mulatta.

Staffing at the Animal Center

It has been very difficult to hire competent employees within commuting distance of the NIH Animal Center. This problem will become intensified in direct proportion to the size of the operation at the Poolesville site.

Program Plans

In cooperation with the Laboratory of Immunology, NIAID, LAB has planned a study of serum proteins of twenty inbred and two random bred strains of mice involving various genetic tests. The breeding program to transfer a gamma globulin allotype from one rabbit strain to another will continue.

DRS, Laboratory Aids Branch, cont'd:

Since several LAB programs are growing at a rapid rate and user identification is established, the logical next step is the transfer of financing to the Service and Supply Fund. The feasibility of an early transfer of certain glassware preparation, media production and animal quarantine and holding functions to the Fund is under study by the Branch and a preliminary proposal will soon be made.

Construction will begin on permanent facilities at the NIH Animal Center, thus permitting the transfer of certain quarantine activities to that location.

Germfree and SPF Production will occupy renovated facilities and develop breeding colonies as rapidly as can be safely accomplished.

A major project for 1963 will be the design of small animal production facilities at the NIH Animal Center.

The emphasis on multidisciplinary approach to disease identification and study will be continued. The number of routine pathology examinations will be further reduced to provide more time for detailed studies of specific diseases.

Serial No. 4.1
1. Laboratory Aids Branch
2. Animal Hospital Section
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A

Project Title: STUDY OF BOVINE OCULAR SQUAMOUS CARCINOMA

Principal Investigator: Dr. Francis Abinanti, NIAID

Other Investigators: William I. Gay, D.V.M.
Mearl Stanton, M.D., NCI

Cooperating Units: Animal Surgery Unit, A.H.S.

Man Years (calendar year 1962):
Total: .10
Professional: .05
Other: .05

Project Description:

Objective: To determine if cancer in the eye of cattle is of virus etiology. To study the pathogenesis of the disease.

Methods Employed: Surgical removal of diseased tissues. Examination of tissues for viral agents.

Proposed Course of Project: The surgical procedures and follow-up have been completed. Dr. Gay has prepared a paper describing the beneficial effects of removing the plaques, which are primary lesions, and covering the denuded corneal scleral surface with a conjunctival flap. Recurrences of the tumor following the flap operation are markedly reduced.

Part B included Yes_____ No X

Serial No. 4.2
1. Laboratory Aids Branch
2. Animal Hospital Section
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A

Project Title: PROSTHETIC REPLACEMENT OF THE FEMORAL HEAD

Principal Investigator: William I. Gay, D.V.M.

Other Investigators: Sara Jane Uhrich, D.V.M.

Cooperating Units: Experimental Surgery Unit, A.H.S.

Man Years (calendar year 1962):
Total: .05
Professional: .05
Other: .00

Project Description:

Objective: To evaluate simple metallic device for replacing diseased or injured femoral heads in the dog.

Methods Employed: One femoral head in each of two dogs was replaced with an accurately designed vitallium prosthesis.

Major Findings: While the metal and design used are too expensive for general veterinary use, it is nevertheless important to assess the tolerance of this metal by animal tissues and the strength of this device as compared to those manufactured of other metals. Since evaluation is not complete, a final report cannot be made at this time.

Proposed Course of Project: Project will be discontinued upon submission of the final report referred to above.

Part B included Yes_____ No X

Serial No. 4.3
1. Laboratory Aids Branch
2. Animal Hospital Section
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A

Project Title: TESTING OF CASTIPLAST 11, 17, AND 327 (RESINS OF THE EPOXY TYPE) IN TISSUE

Principal Investigator: Sara Jane Ehrich, D.V.M.

Other Investigators: William I. Gay, D.V.M.

Cooperating Units: Animal Surgery Unit, A.H.S.

Man Years (calendar year 1962):
Total: .02
Professional: .01
Other: .01

Project Description:

Objective: To determine the suitability of these materials as bone substitutes.

Methods Employed: A section of femur was removed and replaced with a prosthesis formed of Castiplast 327 (trade name of National Engineering Products, Inc.).

Major Findings: The Castiplast 327 prosthesis supported the weight of the dog for approximately one year without adverse effect. Radiographs indicate bone has grown over the plastic.

Part A (Cont'd)

Proposed Course of Project: The producer of Castiplast 327 is no longer in business and the material is not available for further study. Development of a similar plastic by Instrument Engineering and Design Branch, DRS, would permit continuation of this project.

Part B included Yes____ No__X__

Serial No. 4.4
1. Laboratory Aids Branch
2. Animal Production Section
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A

Project Title: RESEARCH IN ANIMAL EQUIPMENT AND FACILITIES

Principal Investigator: Cobert D. LeMunyan, Ed.D.

Other Investigators: Robert S. Runkle, RFPB, DRS

Cooperating Units: Research Facilities and Planning Branch

Man Years (calendar year 1962):
Total: .80
Professional: .80
Other: None

Project Description:

Objective: To develop and evaluate new facilities, techniques, and caging systems for producing or holding experimental animals.

Major Findings: A continuing study and review of current concepts, operating methods, and needs in regard to animal housing facilities and caging systems has been undertaken. Thus far the study has revealed that improved equipment design, development of semi-automated caging systems, evaluation of new materials and design changes of housing facilities are necessary to meet current and future demands for higher quality animals. It was found that present building designs at the NIH were not capable of providing the necessary barriers for "closed" colony production which is in increasing demand, and that caging systems were not adequate for reduction of health hazards and most economical methods of production and holding animals.

Part A (Cont'd)

Under this program several of the changes indicated by the study have been effected. Evaluation of the results promises a demonstrated greater economy in animal production and holding while reducing health hazards to the animal colonies.

Significance: As a result of this continuing program the NIH will develop new concepts, realistic caging systems, and designs for animal facilities which will be capable of meeting the ever increasing and demanding needs of the entire medical community.

Proposed Course of Project: Continuation and expansion of present parameters of the research and development program in animal equipment and facilities.

Part B included Yes____ No X

Serial No. 4.5
1. Laboratory Aids Branch
2. Animal Production Section
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A

Project Title: EFFECT OF HYDROCHLORIC ACID AND CHLORINE TREATMENT UPON PSEUDOMONAS AERUGINOSA AND COLIFORM BACTERIA IN MOUSE DRINKING WATER

Principal Investigator: Charles W. McPherson, D.V.M.

Other Investigators: Damara Bolté, B.S.

Cooperating Units: None

Man Years (calendar year 1962):
Total: .02
Professional: .02
Other: None

Project Description:

Objective: To find a water additive which would inhibit objectionable bacterial growth in animal drinking bottles.

Methods Employed: Cages containing infected mice were divided into two groups. For each group two water bottles were put on each cage, one with tap water, and one with either tap water plus HCl or tap water plus sodium hypochlorite (chlorine) solution. Each water bottle was tested for the presence of P. aeruginosa and coliforms every day for seven days.

Major Findings: Both HCl and chlorine were effective, but chlorine was more rapidly dissipated.

Part A (Cont'd)

Significance: Contaminated animal drinking water bottles are an important reservoir and vehicle in the transmission of *P. aeruginosa* and other infectious agents in animal colonies. Accordingly an additive to prevent such contamination is important. The findings of this investigation were given in a speech presented to the 13th Annual Meeting of the Animal Care Panel in Chicago, Illinois, on October 3, 1962. A paper is being prepared for inclusion in the *Journal of Laboratory Animal Care*.

Proposed Course of Project: Investigation of the effect of chemical additives on the epidemiology of water bottle transmitted diseases.

Part B included Yes_____ No X

Serial No. 4.6

1. Laboratory Aids Branch
   Collaborative Project
2. Animal Production Section and
   Comparative Pathology Section
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A

Project Title: THE EFFECT OF DIFFERENT METHODS OF CONTROL AND THE ADMINISTRATION OF CHEMICALS IN THE DRINKING WATER TO ELIMINATE COCCIDIOSIS FROM A RABBIT COLONY

Principal Investigators: Robert T. Habermann, D.V.M.
Charles W. McPherson, D.V.M.
Rex R. Every, D.V.M. (now at Paige Animal Hospital, La.)
Richard Pierson, B.S.

Other Investigators: None

Cooperating Units: None

Man Years (calendar year 1962):
Total: .6
Professional: .3
Other: .3 (Pierson, Lewis)

Project Description:

Objective: To determine the effect of sanitation, removal of sick animals and cagemates, and sulfaquinoxaline in the erradication of coccidiosis from a rabbit colony.

Methods Employed: Refined and strict methods of sanitation, removal of sick and exposed animals from their cages and rooms, and the administration of sulfaquinoxaline in

Part A (Cont'd)

the drinking water. Weekly fecal samples of each rabbit cage and examination of fecal samples using salt flotation centrifugation technique.

Major Findings: Intestinal coccidiosis was completely eliminated from the NIH rabbit production colony by the methods utilized.

Significance: Coccidiosis was eliminated from the NIH rabbit colony by strict sanitation, removal of infected rabbits and the administration of sulfaquinoxaline in the drinking water. Approximately 100 fecal samples from the colony have been obtained each week since November, 1960, and examined for Coccidia oocysts. None has been positive.

Proposed Course of Project: Completed.

Part B included Yes X No

PHS-NIH
Individual Project Report
Calendar Year 1962

Part B Honors, Awards, and Publications

Publications:

McPherson, C. W., Habermann, R. T., Every, R. R., and Pierson, R.: Eradication of intestinal coccidiosis from a large breeding colony of rabbits. Proceedings of the Animal Care Panel. 12: 133-140, Sept. 1962.

Honors and Awards related to this project:

None

Serial No. 4.7
1. Laboratory Aids Branch
2. Comparative Pathology Section
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A

Project Title: THE GENERATION TIME OF MAST CELLS OF THE RAT

Principal Investigator: Anton M. Allen, D.V.M., Ph.D.

Other Investigators: None

Cooperating Units: None

Man Years (calendar year 1962):
Total: .2
Professional: .1
Other: .1 (Meggers)

Project Description:

Objective: To determine the generation time of mesenteric mast cells of 30-day-old rats. To study means by which mast cells become binucleated and the functional significance of binucleation.

Methods Employed: New combinations of tissue coloring agents (Feulgen reaction with non-metachromatic basic dyes) are utilized to demonstrate mitotic figures in identifiable mast cells. Autoradiography methods are employed in studies of cell generation time.

Major Findings: The generation time of mesenteric mast cells of 30-day-old rats is roughly ten times greater than that of cells of renewal systems (epithelia). Labeled binucleated mast cells appear in the mesentery only after a population of

Part A (Cont'd)

cells has been labeled for a period of time equal to the time required for some of the mast cells to undergo DNA doubling and mitosis.

Significance: The generation time of loose connective tissue cells has not been reported. The mast cell is the only such cell which is easily identifiable. The methods provide a means of studying the generation time of a connective tissue cell in animals of different age and subjected to different experimental manipulations. The findings support the hypothesis that binucleation results from the failure of cytokinesis of cells undergoing mitosis.

Proposed Course of Project: Continuation

Part B included Yes X No

PHS-NIH
Individual Project Report
Calendar Year 1962

Part B Honors, Awards and Publications

Publications:

Allen, A. M.: Deoxyribonucleic acid synthesis and mitosis in mast cells of the rat. Laboratory Investigation. 11: 188-191, Feb. 1962.

_____ Mitosis and binucleation in mast cells of the rat. Journal of the National Cancer Institute. 28: 1125-1151, May 1962.

Meggers, D. E., and Allen, A. M.: Feulgen reaction-Bismarck brown; a stain for mast cells in mitosis. Stain Technology. 37: 221-223, July 1962.

Honors and Awards related to this project:

None

Serial No. 4.8
1. Laboratory Aids Branch
2. Comparative Pathology Section
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A

Project Title: INVESTIGATION OF THE PATHOLOGY OF CYCAD (PLANT FAMILY - CYCADACEAE) TOXICITY IN CATTLE

Principal Investigators: Anton M. Allen, D.V.M., Ph.D.
Olaf Mickelsen, Ph.D., NIAMD
(now at University of Minnesota)

Other Investigators: Roy Kinard, D.V.M.

Cooperating Units: Laboratory of Nutrition and Endocrinology, NIAMD

Man Years (calendar year 1962):
Total: .4
Professional: .2
Other: .2 (Meggers, Faulkner, and Sutton)

Project Description:

Objective: To study the effects of feeding toxic levels of cycad preparations (powdered nut) to calves.

Methods Employed: Cycad nuts were dried, powdered, and fed at 2 and 5% levels in calf rations until the calves died. Ordinary pathology and hematology examinations were performed.

Major Findings: The calves lost weight, developed intermittent incoordination of limbs, and died 23 to 41 days after the onset of feeding. No consistent changes were noted in hemoglobin, packed cell volume, leukocyte, and reticulocyte values.

Part A (Cont'd)

The pathology findings included atony and impaction of the rumen, edema and gelatinous degeneration of loose connective tissues, hemorrhage in fatty connective tissues, severe atrophy and architectural alteration of the liver.

Significance: Detailed histopathology studies of cycad toxicity in cattle have not been reported. No evidence was found of an association between cycad toxicity of cattle and neurological disease in the human population of Guam where cycad flour is used as a source of starch. The pathology of cycad poisoning was reported informally in the transcripts of the proceedings of the Conferences on the Identification of Toxic Elements of Cycads held in February and August 1962.

Proposed Course of Project: Continuation with different approach.

Part B included Yes_____ No__X__

Serial No. 4.9
1. Laboratory Aids Branch
2. Comparative Pathology Section
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A

Project Title: CHRONIC MURINE PNEUMONIA OF THE ALBINO RAT

Principal Investigator: James R. Ganaway, D.V.M., M.P.H.

Other Investigators: None

Cooperating Units: None

Man Years (calendar year 1962):
Total: .30
Professional: .10
Other: .20 (Despeaux and Talley)

Project Description:

Objective: To isolate and characterize the etiologic agents. To perform transmission studies with each suspected agent. To recommend measures for prevention and control of this disease complex under colony conditions.

Methods Employed: Microbiology, immunology, and pathology methods were employed.

Major Findings: Of major importance during the year was the recent installation of Horsfall type filtered air cages for the prevention of horizontal spread of respiratory agents. A small colony of rats free of respiratory pathogens, to be used in future transmission studies, has been re-established in these Horsfall units.

Part A (Cont'd)

Significance: This disease complex is the greatest cause of morbidity and eventual mortality in rat colonies. Affected rats are unfit for research, particularly when destined for long term or toxicity studies.

Proposed Course of Project: Continuation

Part B included Yes_____ No X

Serial No. 4.10
1. Laboratory Aids Branch
2. Comparative Pathology Section
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A

Project Title: MUCOID ENTERITIS OF RABBITS

Principal Investigator: James R. Ganaway, D.V.M., M.P.H.

Other Investigators: Anton M. Allen, D.V.M., Ph.D.
Thomas D. Moore, Ph.D.

Cooperating Units: Animal Production Section

Man Years (calendar year 1962):
Total: .60
Professional: .40
Other: .20 (Despeaux)

Project Description:

Objective: To determine the etiological factor(s). Attempt experimental reproduction of the disease in rabbits. Based on the foregoing, to recommend measures for control or prevention in the rabbit colonies.

Methods Employed: Routine pathological and bacteriological methods were used.

Major Findings: This chronic condition in weanling rabbits smolders endemically in the rabbit colonies. Although sporadic in occurrence, when it does appear, usually the entire litter is affected. While pure culture isolation has not been possible as yet, a heretofore undescribed micro-organism has been observed in roughly 95% of the cases. Attempts to culture this organism are still in progress.

Part A (Cont'd)

Significance: This condition represents the greatest cause of morbidity in our rabbit colonies. Though widely recognized as such throughout the world, etiology has not been ascertained.

Proposed Course of Project: Continuation

Part B included Yes_____ No X

Serial No. 4.11
1. Laboratory Aids Branch
2. Comparative Pathology Section
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A

Project Title: RINGTAIL OF RATS

Principal Investigator: James R. Ganaway, D.V.M., M.P.H.

Other Investigators: Anton M. Allen, D.V.M., Ph.D.

Cooperating Units: Animal Production Section

Man Years (calendar year 1962):
Total: .3
Professional: .2
Other: .1 (Despeaux)

Project Description:

Objective: To characterize this disease in terms of etiology and pathologic anatomy. To reproduce the disease experimentally and to recommend measures for prevention or control under colony conditions.

Methods Employed: Routine pathological and microbiological methods were used.

Major Findings: The condition is smoldering endemically in the general production rat colonies. The lesions are those of a chronic periarthritis affecting the distal joints of the limbs and the joints of coccygeal vertebra. Studies on etiology and disease reproduction are incomplete.

Part A (Cont'd)

Significance:	Essential to our knowledge of the diseases of laboratory animals. Animals so affected are worthless for other research.
Proposed Course of Project:	Continuation

Part B included Yes_____ No__X__

Serial No. 4.12
1. Laboratory Aids Branch
2. Comparative Pathology Section
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A

Project Title: STUDY OF CAUSES OF DEATH IN STRAIN 13 AND STRAIN 2 INBRED GUINEA PIG COLONIES

Principal Investigator: James R. Ganaway, D.V.M., M.P.H.

Other Investigators: Anton M. Allen, D.V.M., Ph.D.
Roy F. Kinard, D.V.M.

Cooperating Units: Genetics Unit, LAB

Man Years (calendar year 1962):
Total: 1.1
Professional: .6
Other: .5 (Despeaux and Talley)

Project Description:

Objective: To define the causes of losses in the inbred colonies of guinea pigs. To isolate the etiologic agent(s). To recommend measures for control or prevention of these losses in the colonies.

Methods Employed: Routine microbiology, pathology (both clinical and anatomic), nutritional, and epidemiology methods were used.

Major Findings: The Strain 13 guinea pig colony faced extinction in March 1962. Through intensive investigation and the development of recommendations for disease control, the colonies now appear to be back in production. The losses were not restricted to any particular age group. Abortions, stillbirths, pregnancy toxemia, deaths of young

Part A (Cont'd)

growing pigs and sexually mature pigs, and premature deaths of older pigs were all encountered. A combination of micro-organisms and dietary deficiencies appear to have played important roles as causes of death.

Significance: The value of the highly inbred guinea pig colonies cannot be estimated monetarily. It appears that the colony has been spared extinction. Several areas of interest derived from this study will be pursued further. From a comparative medicine standpoint, it should be noted that pregnancy toxemia occurs rather frequently in humans and its causes are poorly understood.

Proposed Course of Project: Continuation

Part B included Yes_____ No__X__

Serial No. 4.13
1. Laboratory Aids Branch
2. Comparative Pathology Section
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A

Project Title: A BACTERIOLOGICAL EXAMINATION OF LABORATORY ANIMAL FEED TO DETERMINE THE OCCURRENCE OF PATHOGENS

Principal Investigators: Robert T. Habermann, D.V.M.
Fletcher P. Williams, Jr., B.S.
(now at Pied Piper Farms)

Other Investigators: None

Cooperating Units: None

Man Years (calendar year 1962):
Total: .05
Professional: .05
Other: None

Project Description:

Objective: To determine the occurrence of Salmonella species, and other pathogenic bacteria or mycotic organisms in bags of mouse, rat, guinea pig, and rabbit pellets and in sawdust (bedding).

Methods Employed: Ordinary bacteriological methods for the isolation and identification of bacterial and mycotic organisms.

Part A (Cont'd)

Significance: This study has shown that standard commercial types of animal feed and sawdust are frequently contaminated with enteric organisms, and that these materials are possible sources of salmonellosis in animal colonies.

Proposed Course of Project: Continuation

Part B included Yes X No

PHS-NIH
Individual Project Report
Calendar Year 1962

Part B Honors, Awards, and Publications

Publications:

Williams, F. P., Jr., and Habermann, R. T.:
A study of the bacterial contamination in commercially prepared animal feeds and bedding. Proceedings of the Animal Care Panel. 2: 11-14, Feb., 1962.

Honors and Awards related to this project:

None

Serial No. 4.14
1. Laboratory Aids Branch
2. Comparative Pathology Section
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A

Project Title: THE EFFECT OF PIPERAZINE ADIPATE IN THE DRINKING WATER FOR THREE DAYS TO CONTROL OXYURIDS IN FEMALE MICE AND THEIR LITTERS

Principal Investigator: Robert T. Habermann, D.V.M.

Other Investigators: Fletcher P. Williams, Jr., B.S. (now at Pied Piper Farms)

Cooperating Units: None

Man Years (calendar year 1962):
Total: .2
Professional: .1
Other: .1 (Lewis)

Project Description:

Objective: To determine the effect of piperazine adipate in the drinking water for three days on the removal of oxyurids (pinworms) from female mice and their litters.

Methods Employed: Critical testing of piperazine adipate for the removal of oxyurids.

Major Findings: Piperazine adipate was effective in the removal of oxyurids from female mice and their litters when the females and their weaned litters were re-treated after 30 days.

Part A (Cont'd)

Significance:	Unweaned mice are carriers of pinworms unless treated with piperazine adipate after they are weaned.
Proposed Course of Project:	Completed. A paper (Treatment of Female Mice and Their Litters with Piperazine Adipate in the Drinking Water) is due for publication in the Journal of Laboratory Animal Care in 1963.

Part B included Yes_____ No X

Serial No. 4.15
1. Laboratory Aids Branch
2. Comparative Pathology Section
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A

Project Title: PAPILLARY CYSTIC ADENOCARCINOMA OF THE KIDNEY OF A DOG

Principal Investigator: Robert T. Habermann, D.V.M.

Other Investigators: Fletcher P. Williams, Jr., B.S.
(now at Pied Piper Farms)

Cooperating Units: None

Man Years (calendar year 1962):
Total: .10
Professional: .05
Other: .05 (Faulkner)

Project Description:

Objective: To determine the course of papillary cystic adenocarcinoma of the kidney in a dog after removal and after four years.

Methods Employed: Clinical, gross, and microscopical, and radiological findings in a dog before and after removal of kidney tumor.

Major Findings: The primary renal tumor which was removed surgically, and the metastic tumor found in the posterior abdomen and lungs nearly four years after surgery, had similar histological characteristics. The tumor was classified as a papillary cystic adenocarcinoma.

Part A (Cont'd)

Significance:	Kidney tumors in man and in dogs often metastasize to the abdominal organs and lungs after removal.
Proposed Course of Project:	Completed. A paper entitled "Papillary Cystic Adenocarcinoma of the Kidney in the Dog" has been submitted to the Journal of the American Veterinary Medical Association for publication.

Part B included Yes_____ No__X__

Serial No. 4.16
1. Laboratory Aids Branch
2. Comparative Pathology Section
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A

Project Title: A STUDY OF CHRONIC RESPIRATORY DISEASE IN RATS

Principal Investigator: Robert T. Habermann, D.V.M.

Other Investigators: Fletcher P. Williams, Jr., B.S.
(now at Pied Piper Farms)
Charles W. McPherson, D.V.M.
Rex R. Every, D.V.M.
(now at Paige Animal Hospital)

Cooperating Units: None

Man Years (calendar year 1962):
Total: .30
Professional: .15
Other: .15 (Lewis, Talley, Faulkner)

Project Description:

Objective: To determine the effect of sulfamerazine and broad spectrum antibiotics on the course of chronic respiratory disease in successive generations of rats.

Methods Employed: Ordinary methods of bacteriology, pathology, and long term colony management were used.

Major Findings: Sulfamerazine controlled rhinitis, middle ear infection, and bronchiectasis when offered continuously in the feed and markedly reduced these infections when offered daily in the drinking water.

Part A (Cont'd)

Significance: Chronic respiratory disease (CRD) is a very important disease that infects almost 100% of rats reared in the ordinary rat colony. Sulfamerazine offered continuously in the feed at the rate of 5.0 mg per 20 grams of feed was effective in eliminating CRD from a rat colony.

Proposed Course of Project: Completed. A paper entitled "The Effect of Orally Administered Sulfamerazine and Chlortetracycline on Chronic Respiratory Disease in Rats" has been submitted to the Journal of Laboratory Animal Care for publication.

Part B included Yes_____ No X

Serial No. 4.17
1. Laboratory Aids Branch
2. Comparative Pathology Section
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A

Project Title: A SURVEY OF MYCOTIC DISEASES IN DOMESTIC ANIMALS SUBMITTED BY THE COMMUNICABLE DISEASE CENTER, KANSAS CITY, KANSAS

Principal Investigators: Robert T. Habermann, D.V.M.
Robert W. Menges, D.V.M., M.P.H., CDC, Kansas City

Other Investigators: Rex R. Every, D.V.M.
(now at Paige Animal Hospital)

Cooperating Units: Communicable Disease Center

Man Years (calendar year 1962):
Total: .30
Professional: .15
Other: .15 (Lewis, Faulkner's tissue processing unit)

Project Description:

Objective: To determine the occurrence of blastomycosis, histoplasmosis and other mycotic infections in domestic animals, and to correlate histological and serological findings.

Methods Employed: Ordinary histopathological and serological methods including the flotation antibody techniques were used.

Part A (Cont'd)

Major Findings: Tissues from 174 animals were received for examination. The listing below shows the species, quantity and differential diagnoses:

DOGS - 168		CATS - 4	
Pneumonia	26	Actinomycosis	1
Interstitial Nephritis	9	Pneumonia	2
Filariasis	13	Hepatitis	1
Blastomycosis	7		
Histoplasmosis	5	RABBIT (exper.) - 1	
Neoplasms	10	Histoplasmosis	1
Distemper	4		
Hepatitis	7	COW - 1	
Spirocerciosis	2	Neoplasm	1
Dermatitis	2		
Lymphadenitis	2		
Botryomycosis	1		
Sarcosporidiosis	1		
Tonsilitis	1		
No Significant Lesions	78		

Significance: The findings reveal a high prevalence of and generalized infections of blastomycosis, histoplasmosis, and filariasis. Neoplasms occur frequently in aged dogs and histoplasmosis occurs in pigs and calves.

Proposed Course of Project: Continuation. Two manuscripts are in preparation for publication; they are entitled "A Review and Recent Findings on Histoplasmosis in Animals" and "Isolation of Histoplasma capsulatum from a calf and a pig."

Part B included Yes X No

PHS-NIH
Individual Project Report
Calendar Year 1962

Part B Honors, Awards, and Publications

Publications:

Every, R. R., Menges, R. W., and Habermann, R. T.: Canine blastomycosis in Louisiana. Veterinary Medicine. 8: 707-708, Aug., 1962.

Honors and Awards related to this project:

None

Serial No. 4.18
1. Laboratory Aids Branch
2. Comparative Pathology Section
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A

Project Title: INVESTIGATION OF THE PROBLEM OF URINARY BLADDER STONES IN MICE

Principal Investigator: Roy Kinard, D.V.M.

Other Investigators: None

Cooperating Units: Animal Production Section
Animal Hospital Section

Man Years (calendar year 1962):
Total: .1
Professional: .1
Other: None

Project Description:

Objective: To describe the disease, ascertain the etiology and prescribe an eradication program.

Methods Employed: Ordinary methods of urinalysis, qualitative chemical analysis, minerology, histopathology, radiology and statistics were employed.

Major Findings: A disease characterized by (1) urinary bladder stones composed of magnesium ammonium phosphate, (2) cystitis and pyelonephritis and (3) small body size and excessive culling has been observed and described in certain strains of mice in the NIH production colonies. Several hypotheses concerning etiology have been proposed.

Part A (Cont'd)

Significance: It appears that the eradication of this ailment, or its cause, would reduce appreciably the number of mice rejected for laboratory use.

Proposed Course of Project: Continuation

Part B included Yes X No

PHS-NIH
Individual Project Report
Calendar Year 1962

Part B Honors, Awards and Publications

Publications:

Kinard, R. F.: Occurrence of bladder stones in inbred and hybrid mice. Journal of Urology. 88: 223-226, Aug., 1962.

Honors and Awards related to this project:

None

Serial No. 4.19
1. Laboratory Aids Branch
2. Comparative Pathology Section
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A

Project Title: INVESTIGATION OF A MEANS FOR CLINICAL DIAGNOSIS OF CHRONIC MURINE PNEUMONIA

Principal Investigator: Roy Kinard, D.V.M.

Other Investigators: James Ganaway, D.V.M., M.P.H.

Cooperating Units: None

Man Years (calendar year 1962):
Total: .3
Professional: .1
Other: .2

Project Description:

Objective: To find and evaluate a method, other than direct observation of the characteristic lesions, for the clinical diagnosis of chronic murine pneumonia. A nonspecific method such as serum gamma globulin level may suffice since many laboratory rat colonies are maintained free of infectious disease except chronic pneumonia and because a diagnosis of the absence of the disease would be useful in any case. Therefore the objective during 1962 has been to initiate a project to show a definite proportional relationship between serum gamma globulin level and severity of lesions of chronic pneumonia or to show that animals free of penumonia may be selected by low (normal?) gamma globulin level.

Part A (Cont'd)

Methods Employed: Ordinary methods of autopsy, histopathology and serum protein electrophoresis have been employed.

Major Findings: The rats of the NIH production colonies have a very high incidence of chronic pneumonia lesions. The affected animals have relatively high gamma globulin levels compared to those of unaffected rats. Evaluation of this method as a research and diagnostic tool is not yet complete.

Significance: Until now chronic murine pneumonia was diagnosable only by characteristic autopsy lesions and absence of the disease was known only in dead animals. By serum electrophoresis we may be able to follow the course of the disease in living rats or, at least, to select rats that are free of the disease. This will be useful in further experimentation and in establishing and monitoring disease free colonies.

Proposed Course of Project: Continuation

Part B included Yes_____ No X

Serial No. 4.20
1. Laboratory Aids Branch
2. Comparative Pathology Section
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A

Project Title: FOCAL NECROSIS OF THE LIVER OF RABBITS

Principal Investigator: Thomas Moore, Ph.D.

Other Investigators: James R. Ganaway, D.V.M., M.P.H.
Anton M. Allen, D.V.M., Ph.D.

Cooperating Units: Animal Production Section

Man Years (calendar year 1962):
Total: .4
Professional: .3
Other: .1 (Despeaux)

Project Description:

Objective: To attempt isolation of the etiologic agent(s). To define the lesions. To recommend measures for control or prevention in the rabbit colonies.

Methods Employed: Normal bacteriological and pathological methods were used.

Major Findings: This disease has been recognized only at post mortem examination and is associated with acute enteritis. The lesions in the liver are indistinguisable from those of Tyzzer's Disease of mice. As in Tyzzer's Disease, the intracellular microorganism associated with the liver lesions has resisted all isolation attempts.

Part A (Cont'd)

Significance: Essential to our knowledge of laboratory animal diseases. This condition has not been described heretofore in rabbits. The microorganism associated with the similar syndrome in mice has not been isolated.

Proposed Course of Project: Continuation

Part B included Yes_____ No__X__

December 1962 Calendar Year 1962

PUBLIC HEALTH SERVICE - NATIONAL INSTITUTES OF HEALTH

DIVISION OF RESEARCH SERVICES

Summary of Branch Activities

1. DRS 5
Serial Number

2. Computation and Data Processing Branch
Branch

3. Mr. H. J. Juenemann
Acting Branch Chief

OBJECTIVES

The objectives of the Computation and Data Processing Branch are:

(1) To provide a central computation and data processing service for NIH using electronic digital computers, electric accounting machinery, occillogram scanner, plotters and other data processing equipment.

(2) To provide expert mathematical and statistical assistance in the design, execution, and analysis of experiments and studies in the biomedical sciences.

(3) To plan and conduct developmental work in the application of mathematics, statistics, and data processing methods to biomedical investigations.

PROGRAM

The program of this Branch is to provide a wide variety of professional computation and data processing services in support of biomedical research at NIH. Its activities continue from year to year and are financed through the NIH Service and Supply Fund, and the NIH Management Fund.

The activities of the Branch are not readily classifiable by programs with a definite beginning and end. However, there is in a general sense a logical group of activities associated with each of the three objectives. The first, that of providing NIH with a central data processing service, consumed most of the efforts of the Branch during the year. The second largest group of Branch activities is related to the second of the objectives, that of providing technical consultation to the rest of NIH. Staffing limitations have minimized the amount of effort which could be devoted to the research objective.

ACCOMPLISHMENTS

Of major importance during 1962 was the authorization to double computer capacity by acquisition of a second computer that is compatible with the one now in use. Renovation of Building 12 for installing the second computer began in September 1962, and it is expected that the computer will be operational by March 1963.

The IBM 650, the original computer in the Branch, was released in June 1962 after all major recurring jobs were converted to the H-800 and run in parallel to insure compatibility.

During the year, the Branch continued to process the recurring computer programs for the payroll, many financial and budget records, and supply and property records.

In the scientific and research area, some of the more important computer projects were:

(1) Completion of statistical tabulations for the 8th International Cancer Congress and the Paris Conference.

(2) Evaluation of approximately 70,000 records of blood distribution to select those records which indicated deviation from standards.

(3) A major statistical tabulation program concerning the treatments given prior to termination of extremely large numbers of cancer cases in several states and foreign countries.

(4) Mechanization of the yearly Research Grants Index Publication which will allow a start to be made on general problems of retrieval of substantive information about the nature of the grants program.

(5) Mechanization of a system to automate the control of research grant applications as they flow through various stages of approval and to capture information as a by-product of the real time processing.

Improvement in Services

The program objective of this Branch is to achieve a computation center that is versatile in its ability to perform, responsive to customer needs, easily accessible and widely used. Several steps were taken during the year to achieve this. The scope of the Mathematical Research Unit was broadened to include specialization in softwares and programming systems, training of outside programmers and users, and the addition of an electronic engineer to provide consulting support in systems design and data capturing; a second oscillogram scanner machine and a new horizontal line/point data plotting machine were acquired for the convenience of customers; keypunch machines and electric accounting machines were modernized by standardization of keyboard fonts; an "open-shop" programmer policy was developed to encourage freer use of computational equipment; guided tours were conducted to acquaint visitors with computational and data processing procedures.

Consultation

The Branch serves as the NIH focal point for leadership in the use of computers in medical research. In this role, it advises scientists, administrators, and others concerning the potential of computers for various types of research and administrative applications, assisting them to plan procedures to be followed in developing applications.

During 1962, members of the Branch participated in site inspections with members of the Psychopharmocology Branch of the National Institute of Mental Health to evaluate the proposed contract for the development of a National Clearing House for Mental Health; one Branch mathematician participated in the NIH visiting scientist program by working with a Japanese scientist, thus demonstrating direct CDPB collaboration in the design of research projects; a senior mathematician of the Branch is a member of a Task Group of the American Standards Association Sectional Committee for Computers and Data Processing whose purpose is to standardize the FORTRAN language so that programs written in FORTRAN can be run on machines produced by different manufacturers; the Acting Branch Chief is serving a two year term as Secretary-Treasurer of the Minneapolis-Honeywell H-800 Users Group which meets quarterly to exchange information pertinent to H-800 computers.

The Branch also consults with the Office of the Director, various Institutes and other Public Health Service organizational units concerning computation and data processing equipment needs.

Training and Staff Development

The Computation and Data Processing Branch is placing major emphasis upon training to overcome the difficulties encountered in recruiting and building an adequate staff to support the computer operations. All mathematicians and programmers entering on duty during 1962 were without previous experience but were well educated in mathematics. The Branch developed a three week training course entitled "An Introduction to Computer Programming", that was attended by all new Branch mathematicians and several other outside users. The course included site visits to the equipment floors and specialized instructions by representatives of Minneapolis-Honeywell and the more experienced members of the Branch staff. Other forms of training included the short-course technique in the specific topics of language, programs and application of mathematical principles or theories; programming courses sponsored by Minneapolis-Honeywell; and participation in the Customer Education Center sponsored by International Business Machines Corporation.

In addition, Branch staff members have attended numerous conferences to exchange technical information and to improve their ability to meet NIH computer service needs. These include conferences of the Honeywell H-800 Users Group, meetings of the Biomedical Information - Processing Organization, the Interagency Committee on Automatic Data Processing, the NIH Steering Committee on Data Processing, the Public Health Service Data Processing Chiefs, and the Eastern Joint Computer Conference.

Equipment Use

As the H-800 computer has been the sole computational since June, 1962, it has operated on an average of 20 hours per day, six days per week, and even though this amount of time was utilized, it was still necessary to obtain services from outside sources to meet deadlines on certain jobs.

During the first half of 1962, the H-800 computer ran in parallel with the

IBM 650. As already stated, the latter was released in June, 1962, and shortly thereafter the workload scheduled for computer application made it apparent that additional equipment would be necessary to meet the demands. Action was initiated to obtain authority to rent an additional computer and to renovate the building to house it.

The EAM equipment and Key Punch machines are operated for one full shift per day and an additional quantity of overtime use averaging about 25% of a normal work day. The quantity of work for the amount of equipment and the availability of personnel necessitates utilization over and above the normal 40 hour week.

Personnel

The number of employees increased during 1962 to meet the increased workload. At the beginning of the year, the average Branch strength was 100 people; at the close of the year it was approximately 140. Although this is a significant increase, virtually every unit in the Branch will need more personnel to meet the still heavier workload resulting from the installation of additional computer equipment. As examples of this, by the close of the current Fiscal Year, we hope to add fifteen programmers and mathematicians, four computer console operators, four EAM operators, three clerical employees, two key punch operators, and a project planner. These would be in addition to the present staff and would not provide for attritional losses.

Obtaining experienced personnel is exceedingly difficult. Consequently, a continuing effort will be made to seek out the best qualified candidates to fill the needs of the Branch and to develop training programs to make the new employees as productive as possible in a relatively short period of time.

Major Problems

The Branch faces two major interrelated problems: recruitment and training difficulties and a shortage of space. During 1962, the Branch grew about 40% in the number of employees, yet acquired only 3890 square feet or 23% of additional space. To further complicate space problems, the renovation of Building 12 to accommodate the second computer requires utilization of approximately 1400 square feet of office space, which in turn means more crowded conditions in remaining office areas.

February 1963 Calendar Year 1962

PUBLIC HEALTH SERVICE - NATIONAL INSTITUTES OF HEALTH

DIVISION OF RESEARCH SERVICES

Summary of Branch Activities 1. DRS-6
Serial Number

2. ENVIRONMENTAL SERVICES BRANCH
Branch

2. Ronald E. Bales, San. Engr. Dir.
Branch Chief

Objective

The objective of the Environmental Services Branch is to stimulate the provision of satisfactory environmental conditions for personnel, animals and equipment used at NIH and its field stations.

Program

The program of the Branch is designed to achieve its objective by studies of special environmental problems, documentation of the data, development of corrective systems, and formal recommendations for corrective action to the research management staff.

The program is concerned with the environmental conditions in the facilities of the NIH Institutes and Divisions, and provides a variety of consultative services as well as several routine services. It includes detailed studies, surveys and library research to obtain information required to provide practical consultation and to diagnose environmental problems.

Two interrelated and coordinated activities implement the Branch program. These are the environmental engineering and the environmental sanitation activities. The first provides professional services in facility and equipment design and development, heating, ventilating and air conditioning, industrial hygiene, and sanitary engineering. The second provides professional service in microbiology, insect and rodent control, chemistry, and general sanitation.

These two activities work cooperatively in performing the following major functions:

1. Plans for new construction or alterations are reviewed, and environmental control defects are identified and recommendations made for correction in the planning stages.

2. Surveillance is maintained over environmental factors which influence patient and employee health and comfort. This includes special studies of ventilation, air pollution, hospital and laboratory chemical or infectious contamination, odor control, waste handling and disposal systems, water supplies, food supplies and food processing, sound and vibration control, etc.

3. Surveillance is maintained over the insect and rodent control problems at NIH. Infestations are prevented or minimized through a coordinated sanitation program and a regularly scheduled application of insecticides and maintenance of rodent traps and poison bait stations.

4. Performance of environmental control equipment and the quality of related materials are maintained and improved by study and analysis of operations using sterilizers, distilled water systems, glassware washers, laboratory hoods, and ventilation systems, floor and wall cleaners, building materials, detergents, and the like.

5. New equipment, processes and procedures for environmental control are conceived, developed, and tested for use, including isolation systems, research animal housing and facilities, disinfection sterilization procedures, germfree and specific pathogen or virus free animal facilities, and waste treatment systems.

6. Surveillance and consultation services are provided for the assessment and control of biologic agents in the production and research use of SPF and germfree animals.

7. Special environmental control services are performed where extraordinary needs exist, such as chlorination, chemical or biologic decontaminations, gas and beta-ray sterilizations, special bacteriologic or other bio-assays, water or material analyses, special sanitation inspections, training lectures or demonstrations, etc.

Summary of Progress and Accomplishments

Engineering Section

The engineering staff devoted much of its time to consultations which deferred a number of studies scheduled to be finished this year. For example, development work on special research environments, isolator units and ventilation studies has been deferred to accommodate the consulting work. Engineering data for germfree animal isolator components was developed during the year, and a transfer cylinder method for introducing sterile supplies into plastic germfree animal isolators was perfected. A performance study of the NIH Animal Center sewage oxidation lagoon at Poolesville, Maryland was continued during the year and is providing data for the design and operation of a planned larger installation of the same type at the Center. A study and report were completed on air pollution from the NIH power plant and incinerator stacks.

The Research Facilities Planning Branch laboratory mock-up was used to appraise the effectiveness of various laboratory ventilation alternative designs. Also ventilation surveys were conducted on two of the research laboratory buildings on the reservation.

The requirements, plans, and specifications for several new construction and major alteration projects were reviewed and text material was provided for a projected NIH laboratory design standard.

Consultations included provision of functional requirements and purchase specifications for many equipment items and facilities. These included cage washer, isolators, incinerators, autoclaves, floor washing machines, controlled temperature cabinets, water filters, deionizers, biological safety rooms, etc.

Other consultations were provided on lighting and ultraviolet installations, toxic vapor controls, factory acceptance tests and inspections on new isolators, evaluation of counter tops, and other materials of construction, etc.

Services provided included several chlorinations of water cooling towers, water tanks, and supervision of chlorination of all new and reworked water mains. Also, several viral and bacterial decontaminations of animal rooms and trucks were accomplished using beta propiolactone and, in one animal room, development and use of a steam-formaldehyde system. Ethylene oxide sterilizations were performed on many small items as required and beta-ray sterilizations were done on germfree animal diet and other special items.

Sanitation Section

The sanitation inspection program was expanded during 1962. The program has proven to be very effective in showing sanitation defects and in developing improvements. It should, however, be expanded to allow more frequent, broader, and more complete coverage of the total environment. Routine inspections were done in animal rooms, laboratories, patient areas, surgical operating suites, barber and beauty shops, laundry, and food services. Also completed were surveys of the dental clinic and autopsy rooms.

An extensive reservation-wide study of the handling and disposal of waste materials was completed. It was concluded that present waste handling practices are unsatisfactory because of a general lack of compliance with standard procedures. This lack of compliance appears due to two main causes: a lack of specific assignment of responsibility for waste handling in the research staff and the lack of a satisfactory type of container for handling infectious wastes.

The study concluded with a recommendation for the use of combustible water-proof, flame-resistant paper bags. Quantitative and qualitative measurements of bacteria in operating rooms during surgery, sanitary and bacteriologic surveys of nursing areas that have infection problems, and special bacteriologic studies of water supplied and water uses in patient areas have been made to evaluate and reduce environmental cause of infections. A study of hydrojets used in patient areas revealed that sterilization of these units is necessary within five day intervals to prevent contamination of the room air with flavobacteria. Further, a study of water storage indicated that flavobacteria survive 1-10 ppm chlorination and will continue to grow and multiply after the chlorine has disappeared.

The common prevalence of pseudomonas infections in laboratory animals was established by finding that these organisms existed in many animal drinking water bottles. Methods are being developed for isolating and identifying these organisms, especially Pseudomonas aeruginosa, from the feed, feces, and water from animal production colonies. Because of the impact on research results, control of these organisms is an immediate necessity.

A surface soil meter invented by Robert J. Weatherby, an EOB sanitarian, is very effective in evaluation of the degree of cleanliness of floors and other surfaces.

Routine animal room surveys, covering over 200 animal rooms, provided information on the extent of insect and rodent harborages, viable contamination of drinking water bottles, effectiveness of various types of disinfectants used, a census of total animal population, as well as descriptions of sanitation deficiencies and recommendations for corrections.

In addition to the inspections of bakeries and dairy plants, several feed mills bidding on animal feed contracts were inspected. The food production processes showed many deficiencies in sanitation which could cause disease or improper hormonal activity and nutrition in research animals. This program of inspection and general tightening of procurement requirements should be supported and pursued with vigor.

The specific pathogen-free mouse colony in the Laboratory Aids Branch has been kept under bacteriologic surveillance throughout the year, providing valuable experience and data for future maintenance and research use of such animals.

Insect and rodent control services were increased during 1962 by the addition of operations in the new Buildings 29, 30, 31 and at the expanding NIH Animal Center.

The control activities have been successful in maintaining a low level of infestation in areas where sanitation and physical conditions of harborage are also well controlled. An increased effort has been made to improve sanitation in animal rooms, laboratories, and food handling areas as well as to correct structural defects. It is recognized that the cockroach population in certain areas is the major problem and developmental work on attractant baits has been initiated. Identification of the powerful attractant in stale beer is being investigated.

As new insecticides have become available, they have been tested for toxicity levels on test animals as well as for their effectiveness on various species of insects.

The use of automatic box traps for controlling escaped test animals in the Clinical Center was initiated and results indicate that these can replace spring traps now in use and can provide adequate weekend coverage.

Wasps were encountered in several buildings and efforts to eliminate them were not completely successful.

Publications

1. Jaworski, Norbert A., and Miller, Carl E., DVM: "Refinement of the Cylinder Technique for Supplying Germfree Plastic Isolators." Proceedings of Third Symposium on Gnotobiotic Technology, LOBUND Laboratories, Notre Dame University.

2. Halitsky, James, and Jones, Herbert H.: "Wind Tunnel Tests of Exhaust Ventilation at the NIH Clinical Center." May 1, 1962.

3. Gates, Albert S., Jr.: "Air Revitalization in Sealed Shelters." Proceedings of ASHRAE Symposium on the Air Conditioning of Shelters. June 28, 1962.

Major Problems

Greater effectiveness and efficiency of Branch operations are hindered by the following problems:

1. The Branch laboratory needs a higher level of professional competence in chemistry to deal with complex environmental problems.

2. Retrieval of reference material is presently in a poor state within the Branch, and information from other Branch reference libraries is not adequate. Development of a usable Branch and/or inter-branch system of information identification and retrieval is needed.

3. The Branch has inadequate staff at present to carry out a reasonable number of special studies and to provide consultation services on short-term day-to-day problems in environmental engineering and sanitation.

Two positions have remained vacant this year due to lack of funds. The bacteriological and chemist staff is the area of greatest deficiency.

4. Additional engineering staff is needed to conduct development and testing without decreasing direct consultation services. Two additional persons will be needed when engineering laboratory space becomes available in the testing area in Building 10 after the Germfree animal program is moved to 14G.

January 1963 Calendar Year 1962

PUBLIC HEALTH SERVICE - NATIONAL INSTITUTES OF HEALTH

DIVISION OF RESEARCH SERVICES

Summary of Branch Activities

1. DRS-7
Serial Number

2. RESEARCH FACILITIES PLANNING BRANCH

3. W. B. Page
Acting Branch Chief

Objectives

The major objective of this Branch is the coordination of the planning and construction of new facilities on the NIH Reservation, Bethesda, and at its field stations. This is supplemented with a secondary objective of providing development engineering services and library research where special problems in design are encountered. A satellite of the NIH Library is maintained to provide services to those elements in the Division of Research Services directly concerned with new facilities. The branch staff consists of 22 professional and 9 clerical personnel.

Programs

Design

The design program consists of a staff of professional engineers who coordinate the activities of contract architects, Public Buildings Service liaison architects, NIH research staff members for whom facilities are being provided, and the other engineering branches of the Division of Research Services. The design program is primarily responsible for determining that new construction provides for the program needs of NIH research scientists.

Construction

The construction program provides a close technic[illegible]ntrol of the development of new facilities for NIH during the construc[illegible]n phases. A staff of construction management engineers maintain surveillance during the process of construction to determine that the facility as actually built will conform with the needs of the NIH research staff.

Development

The development program supports the design and construction programs by conducting short-term research and development engineering studies to provide the design which most nearly meets the requirements of the research program. This program also includes a supplemental program of inter-discipline education for staff engineers in fundamental knowledge of biology and the life sciences. A reference library is maintained in support of the educational program and the development program.

Summary of Branch Progress

The design program of the Branch has included 14 projects during 1962. Working drawings have been completed for one project, tentative drawings have been completed for two projects and diagrammatics have been completed for two projects. Programs of Requirements have been completed for five projects and are in the process of being prepared for the remainder. The total 1962 design program involved 66 million dollars worth of construction.

Five major construction contracts were completed during the year. They were: New Surgical Wing - Building #10-A (Exclusive of Instrumentation), Extension of Refrigeration Plant - Building #11-C, Cage Washing Facilities - Building #14-F-1, General Office Building #31 - Parking and Miscellaneous Contracts, and National Library of Medicine - Building #38. Three minor construction contracts were started during the year. They are: NLM Road and Allied Sidewalks, NLM Medlars, and Surgical Wing - Building #10-A - Instrumentation. One minor construction contract, the NIH Animal Center Wells, was started and completed during the year.

The development program has provided guidelines and criteria for the design of health research facilities in the form of brochures and special reports. Primary attention during 1962 was given to specific design problems in the present multi-million dollar construction program of additional facilities underway at NIH. The satellite library, established in the Branch in November, 1960, has worked intensively in support of developmental engineering research investigations, with particular emphasis on the compilation of bibliography and reference services.

Accomplishments

Design Program

NIMH/NINDB Building

The Architect/Engineer revised his diagrammatics which were submitted in October 1961 and re-submitted in February, 1962. He was instructed to proceed with the tentatives in July 1962, after the multi-level parking facility and separate cafeteria building were deleted. The tentative plans were submitted on November 7, 1962, and the review and approval of this stage had not been completed by December 31. A delay was incurred during the review of the tentative plans because the Architect/Engineer cost estimate at this stage exceeded available funds. A review of the cost estimate by Public Buildings Service was in disagreement with the Architect/Engineer's cost estimate and it was decided that the project could be constructed with the funds authorized. The total cost for the project is estimated at $9,239,000, including planning and General Services Administration administrative costs. If our present design schedule is maintained, construction for this project will be started in the last quarter of 1963.

Cancer Research Facility

This project is combined with the NIMH/NINDB Research Laboratory Building and it follows the same schedule. The tentative plans were submitted in November 1962 and a delay was incurred due to the Architect/Engineer's cost estimate exceeding available funds by 14%. A review by Public Buildings Service of the cost estimate indicated that the construction cost would be considerably below the Architect/Engineer's estimate. It was agreed that the project could be constructed within the appropriated funds. The total cost is estimated at $9,480,000, including planning cost and General Services Administration administrative costs. Construction will be started in the last quarter of 1963 if our present design schedule is maintained.

NCI-NIMH/NINDB Cafeteria Building

This project was originally included as a function within the Cancer Research Facility now under design. As the food service needs were more clearly identified, it became necessary to plan for a larger cafeteria to be located outside of the research laboratory buildings. Since this established a new project, it was necessary to obtain Congressional approval to proceed with the design. The site selected for the cafeteria is in the area between the NCI Building and the NIMH/NINDB Building. This location is also convenient for employees in the Biologics Standards and Dental Buildings. The total gross area of the facilities is estimated at 21,000 square feet and the total cost, including planning, is $800,000. The Program of Requirements has been prepared and primary diagrammatics plans have been completed. The present design schedule provides for completing the working drawings by October 1963 so that construction can be coordinated with the NCI-NIMH/NINDB Complex.

NIH Animal Center Phase I

Design of this project is nearly completed and the construction bids are scheduled to be advertised and the contract awarded in time to begin construction in April 1963. The Architect/Engineer initiated work in May 1961 and the final working drawings were completed in November 1962. The project includes the Farm Animal Building, a kennel building, two residences, and the central power plant and utilities to support the structure. The estimated cost is $2,654,000 for construction and $190,000 for planning.

NIH Animal Center, Phase IA

The Program of Requirements for the project was completed and sent to the Bureau of the Budget for approval in April 1962. The design of this project was not initiated in 1962 due to a failure to agree on the scope with the Bureau of the Budget. The project included a primate wing and research facilities for the NIMH. A conditional approval for reduced program was received from the Bureau of the Budget in July 1962. However, by the end of the calendar year the limit of funds and gross area for the facility had not been officially decided and no progress on development of plans had been made.

NIH Animal Center, Phases II and III

Limited progress was made on this project during 1962. Planning funds were made available in the FY 1963 budget and construction funds are programmed for FY 1965. The facilities planned under these two phases amount to approximately $8,000,000 and include a third wing to the animal building, cages for the caged animal wing, agricultural management building, a third residence, small animal production facilities, a hazardous operations laboratory, a waste chemical disposal plant and supporting utilities for these operations. It is expected that design work will be started on these two phases in January or February of 1963. It will be necessary to decide the scope of work in Phase IA before design can proceed with these later two phases.

NIH Office Building Extension

Funds amounting to $700,000 were provided for the design of this project in FY 1962. The Program of Requirements was completed and approved by NIH early in calendar year 1962 for a total of $7,000,000, including $5.5 million for the building and $1.5 million for parking facilities. Approval of the Program of Requirements was delayed by DHEW and the BOB pending resolution of the means by which parking facilities would be provided. In November 1962, an agreement was reached to proceed with the design of the building extension without any parking facility. A revised Program of Requirements was transmitted to the BOB in December 1962 with a request for apportionment of planning funds. It is expected that the design contract can be negotiated in January 1963.

Extension of the NIH Master Utilities Systems

Planning funds for the extension to the utilities systems were provided in FY 1962 and $4,850,000 was appropriated in FY 1963 for construction costs. An Architect/Engineer firm completed a master site plan study and report in December 1962 and the Program of Requirements for the extension to the NIH Utilities Systems was completed in December 1962. This program consists of two phases. Phase I includes the utilities required to support the current construction program consisting of the Cancer Research Building, the NIMH/NINDB Building, the Biologics Standards Building Extension, the NIH Office Building Extension, the fourth extension to the Air Conditioning Plant, the Central Services Building #12 extension, the renovation of the old Cancer Building #6, and the corrections of deficiencies in existing utilities systems. This first phase will cost an estimated $5,144,600 including planning and construction.

Phase II of the Master Utilities Extension Program provides those utilities required to serve the remaining buildings scheduled in the NIH Master Plot Plan and the cost is estimated to be $4,514,400.

Gerontology Building

Planning funds were provided for this project in FY 1962 amounting to $1,000,000. A POR was completed in March of 1962 and revised in June 1962.

The POR was approved by the BOB with total cost of construction limited to $7.5 million in December 1962. The original POR provided for 210,000 gross square feet. At the end of 1962 the POR was being reviewed to determine the priority for reductions in scope. The Architect/Engineer will be requested to provide as much space as possible for $7.5 million, including planning and General Services Administration administrative costs. The selection and negotiation of an Architect/Engineer contract is scheduled for the first quarter of 1963 and the design will be completed in September of 1964. Construction bids will be advertised approximately December 1964, with construction completed in April 1967.

Central Service Building 12 Extension

The FY 1963 appropriation provided $1,800,000 for planning and construction costs involved in altering and extending Central Service Building #12. The POR was completed in August 1962 and approval was obtained from DHEW and GSA for NIH to proceed with the administration of the design and construction. The alteration phase was scheduled to be completed in November 1963 to provide for the installation of the second computer. The design and construction of the extension was scheduled to be completed in October 1964. The A/E contract for the design of the alteration and extension was negotiated in December 1962.

Division of Biologics Standards Extension

Planning funds of $200,000 were allocated in FY 1962 and supplemented with an appropriation of $150,000 in FY 1963 to plan this facility. Construction funds of $4,300,000 have been requested for the 1964 appropriation. The Program of Requirements was completed in March 1962 and after FY 1963 funds became available the design contract was negotiated in October 1962. The diagrammatic plans were reviewed in December 1962 and are scheduled to be formally submitted in January 1963. The design is scheduled to be completed in October 1963, and construction completed in June 1965.

Puerto Rico Perinatal Laboratory

An appropriation of $600,000 is provided for this project in FY 1963. Confusion in the preparation of the justification of this project resulted in insufficient funds for the scope of work involved. This problem was referred to the DHEW and the BOB during 1962 and it was agreed to supplement the original appropriation with an additional $250,000. A Program of Requirements for the project was partially completed in 1962 and will be completed in early 1963 to provide 26,000 gross square feet at a cost of $850,000. The schedule provides for completing the design in December 1963 and completing construction in July 1965.

Basic Research Laboratory Building, Lexington, Kentucky

Funds amounting to $350,000 were appropriated for this project in FY 1961. The project was designed by an architect under contract to GSA and placed

on the market for bids in June 1962. The cost estimate prepared with the completed working drawings exceeded available funds by approximately $50,000. An additional $50,000 was apportioned by the BOB. However, the lowest bid received was approximately $80,000 above the total available funds. The project research program was reviewed by the NIMH and a new POR prepared in the Fall of 1962. A new cost estimate was prepared with the cooperation of PBS and at the end of 1962 arrangements were being made to negotiate another design contract based on a POR providing approximately $320,000 for the construction contract and a gross area of 12,000 square feet. It is estimated that this design will be completed and construction contract awarded during the third quarter of 1963. Construction should be completed in late 1964.

National Library of Medicine MEDLARS

This project was designed in 1962 and the construction contract was awarded in November 1962. Funds were made available in the appropriation for the construction of the NLM. The construction contract is for $187,400 and is scheduled to be completed in June 1963.

Construction Program

New Surgical Wing - 10A

The prime construction contract (GS-R3-B 6434) was completed on January 31, 1962, thirteen months behind the scheduled completion. Slow submittal of shop drawings from several financially handicapped subcontractors, and the bankruptcy of the general contractor in the latter stages of the contract period contributed to this delay. The five major reservation items which were originally scheduled to be accomplished by change orders to the prime contractor were deferred because of the unrealistic estimates submitted. The Contract for the Construction of Reservation Items was assembled and awarded on April 30, 1962 to a new general contractor. Work was completed on this contract on December 21, 1962, approximately two months behind the scheduled completion. Partial occupancy of the building, exclusive of surgical areas, is expected by January 2, 1963.

Building #10-A - Surgical Wing (Instrumentation)

The original instrumentation design was altered to include the most recent developments in instrumentation development. These changes and the search for the latest design required most of fiscal year 1962 for negotiations with five prospective instrumentation contractors. All contracts were awarded by June 29, 1962 and have resulted in some delay in the reservation contract because of slow design and installation of structural supports in the ceilings and walls for the instruments.

Building #11-C - Extension to Central Refrigeration Plant

The contract was completed on July 13, 1962, twelve months behind the scheduled completion. This was primarily a result of slow submittal of shop drawings, slow delivery of the refrigeration equipment and subsequent problems

with the equipment balancing and adjusting required to provide satisfactory performance.

Building #14-F-1 - Cage Washing Facility

The contract was completed on August 8, 1962. The contract schedule was met and this success was mainly due to good coordination between the Government construction engineer on the job and the general contractor.

Building #31 - General Office Building

The building construction for occupancy was completed on October 24, 1961. This included five months delay which primarily was a result of slow submittals of shop drawings and poor coordination of trades on the part of the general contractor. Work continued after the October occupancy of the building on the exterior improvements including the parking facilities, landscaping and miscellaneous utility systems. The miscellaneous work was terminated with the completion of the temporary on-grade parking lot on June 26, 1962 and the additional sidewalks on August 16, 1962.

Building #38 - National Library of Medicine

The building was completed on July 10, 1962. This included a ten month delay which resulted from poor coordination by the contractor and subcontractors in the excavation and removal of the subgrade rock formation.

Development Program

Several studies and investigations of direct application to the design of new NIH facilities were completed during the year and others were initiated. Administrative arrangements were established to provide supportive consulting services to the new Division of Research Facility and Resources. A research development contract was negotiated with a local engineering firm for the design and fabrication of proto-type equipment needed by the development engineering program. Several informal reports were completed and prepared for distribution. These included (1) planning for health research facility; (2) laboratory animal housing; (3) five special engineering studies: a) air-supply fume hood evaluation, b) reducing solar heat gain in buildings, c) vibration limits for operation of electron microscopes, d) resilient floor coverings, e) design criteria for the Electron Microscopy Suite. Engineering studies scheduled for completion in early 1963 include: a) improved vibration standards for design of Electron Microscopes (NINDB), b) laboratory casework layouts for NCI-NIMH/NINDB Buildings, c) application of plastic waste pipes at NIH, d) criteria for distilled water systems (ESB & PEB), e) improvement of laboratory casework standards (PEB), f) laboratory air distribution (ESB).

A collaborative development engineering project has been established with the Laboratory Aids Branch to improve animal care facilities.

NEW CONSTRUCTION 1962

Building	A/E	Plans Completed	Contract Awarded	Contractor	Amount In Thousands	Completion Date*	% Complete 1/1/63	Construction Schedule (Months)	Contract Overrun (Months)**
Surgical Wing (10-A) CCRI	York & Sawyer	2/13/62	4/11/62	Thomas Concrete Construct. Co.	249,500 1/	11/26/62	100	6.5	2
Surgical Wing (10-A) Instr.	NIH-IEDB	3/ 1/62	6/26/62	Sanborn Co. Electronics for Medicine Maysco Westinghouse	488.5	4/30/63	60	13	0
Power Plant (11-C)	Nottingham Associates	9/ 9/60	11/28/60	W.G. Cornell Company	1,125	7/13/62	100	12	8
Cage Washing(14-F-1)	PBS	4/ 1/61	7/ 4/61	Victor Beauchamp	523	8/ 8/62	100	13	0
Genl. Office Bldg. (31) Misc. Contracts	Keyes, Lethbridge & Condon & Collins Associates	5/11/59	9/ 4/59	Norair Engineering Corp.	9,925	8/ 8/62 2/	100	21	13

NEW CONSTRUCTION 1962 (continued)

Building	A/E	Plans Completed	Contract Awarded	Contractor	Amount In Thousands	Completion Date*	% Complete 1/1/63	Construction Schedule (Months)	Contract Overrun (Months)**
National Library of Medicine (38)	O'Connor & Kilham	------	6/ 2/59	A. Venneri Company	7,300	7/10/62	100	24	10

1/ Exclusive of $488,466 for Instrumentation Contracts.

2/ Building completed for occupancy 10/24/61, Miscellaneous contracts.

* By terms of the contract.

** Delay beyond the completion date.

RFPB - 1962 Program of Authorized Design Projects

Project	Design Completion Date	Constr. Completion Date	Constr. Cost	Planning Cost	Total Project Cost	A/E Designer
NIMH/NINDB Bldg.	12/63	8/66	$8,620,000	$ 619,000	$9,239,000	SH&GA, Inc.
Cancer Research Bldg.	12/63	8/66	$8,867,000	$ 613,000	$9,480,000	SH&GA, Inc.
NCI-NIMH/NINDB Cafeteria Bldg.	Not available	Not available	$ 757,000	$ 43,000	$ 800,000	SH&GA, Inc.
NIH Animal Center, Phase I	12/62	6/64	$2,654,000	$ 190,000	$2,844,000	HSM&M
NIH Animal Center Phase IA	10/63	2/65	$1,613,000	$ 125,000	$1,738,000	Not available
NIH Animal Center, Phase II & III	7/64	5/66	$7,327,000	$ 507,000	$7,834,000	Not available
NIH Office Bldg. Ext.	2/64	10/65	$7,000,000	$ 700,000	$7,700,000	Not available
NIH Master Utilities Ext. Phase I	11/63	4/66	$4,784,600	$ 360,000	$5,144,600	Not available
Phase II	N/A	N/A	$4,199,400	$ 315,000	$4,514,400	Not available
Gerontology Bldg.	8/64	3/67	$7,500,000	$1,000,000	$8,500,000	Not available
Bldg. 12 Ext.	10/63	10/64	$1,640,000	$ 160,000	$1,800,000	Not available
Bldg. 29-A, DBS	11/63	10/65	$4,300,000	$ 350,000	$4,650,000	SH&GA, Inc.
Puerto Rico Perinatal Lab.	N/A	N/A	$ 790,000	$ 60,000	$ 850,000	Not available
Basic Research Lab.NIMH			$ 348,000	$ 26,000	$ 374,000	Not available
	Total				$65,468,000	

PUBLIC HEALTH SERVICE - NATIONAL INSTITUTES OF HEALTH

DIVISION OF RESEARCH SERVICES

SUMMARY OF BRANCH ACTIVITIES

1. DRS-8
SERIAL NUMBER

2. INSTRUMENT ENGINEERING AND DEVELOPMENT BRANCH
BRANCH

3. DR. FRED ALT
BRANCH CHIEF

OBJECTIVES

TO RENDER ENGINEERING AND TECHNICAL SUPPORT TO THE INTRAMURAL SCIENTISTS AT NIH THROUGH CONSULTATION AND ADVICE ON ENGINEERING METHODS AND INSTRUMENTATION SYSTEMS APPLICABLE TO CLINICAL AND LABORATORY MEDICAL RESEARCH, AND THROUGH DESIGN, CONSTRUCTION, AND MAINTENANCE OF NON-STANDARD SCIENTIFIC INSTRUMENTS.

TO COOPERATE WITH BIOMEDICAL ENGINEERING ACTIVITIES OUTSIDE NIH; TO DISSEMINATE INFORMATION ON NEW DEVELOPMENTS; TO SUPPLY UNIVERSITIES, RESEARCH INSTITUTES, COMMERCIAL AND NON-PROFIT ORGANIZATIONS OUTSIDE NIH WITH ENGINEERING AND TECHNICAL KNOWLEDGE AND WITH RECOMMENDATIONS ON ORGANIZING BIOMEDICAL ENGINEERING SUPPORT FACILITIES; TO STIMULATE INTEREST AMONG SCIENTISTS, ENGINEERS, AND STUDENTS BY PRESENTING A CLEAR PICTURE OF THE BIOMEDICAL ENGINEERING FIELD, ITS IMPORTANCE TO MEDICAL PROGRESS, ITS CAREER OPPORTUNITIES, AND ITS EDUCATION REQUIREMENTS.

PROGRAMS

THE SPECIFIC PROGRAMS OF THE BRANCH ARE DESIGNED TO ACHIEVE THE BASIC OBJECTIVES DESCRIBED ABOVE.

INTRAMURAL SUPPORT IS PROVIDED BY A STAFF OF ENGINEERS WITH DIVERSIFIED EXPERIENCE IN SEVERAL ENGINEERING AND LIFE SCIENCE DISCIPLINES. THE BRANCH PROGRAM CALLS FOR ORGANIZATIONAL

FLEXIBILITY TO ADJUST THE METHOD OF ITS SUPPORT TO THE PARTICULAR NEED OF THE REQUESTOR (FOR INSTANCE, FULL-TIME OR PART-TIME TEAMWORK WITHIN THE RESEARCH LABORATORY, INDEPENDENT CONSULTATION SERVICES REMOTE FROM THE LABORATORY, ENGINEERING LIAISON BETWEEN INVESTIGATOR AND OUTSIDE CONTRACTOR, AND COOPERATION WITH ENGINEERS AND TECHNICIANS OF INDIVIDUAL LABORATORY STAFFS). OF EQUAL CONCERN IS FLEXIBILITY OF SUBJECT MATTER: THE PROGRAM CALLS FOR THE ENGINEERING STAFF TO COVER THE MANY NEEDED SPECIALTY FIELDS AND TO ACQUIRE KNOWLEDGE IN NEW FIELDS AS THEY DEVELOP (FOR INSTANCE, NEW ULTRASONIC DEVELOPMENTS, LASER APPLICATIONS, BIOMAGNETISM, ETC.).

ANOTHER BRANCH PROGRAM RELATED TO INTRAMURAL SUPPORT IS NOW UNDER STUDY AND DEVELOPMENT: THE INCREASING COMPLEXITY OF MODERN MEDICAL RESEARCH INSTRUMENTATION REQUIRES EVER GREATER ENGINEERING KNOWLEDGE AND EXPERIENCE FOR ITS OPERATION, FOR FAILURE DIAGNOSIS, AND FOR PROGRAMMED PREVENTIVE MAINTENANCE. THE BRANCH IS DIRECTING ITS ATTENTION TOWARD PROVIDING SATISFACTORY, HIGH-QUALITY SERVICE IN THIS AREA. IT ACQUIRES PARTICULAR URGENCY DURING SURGICAL OPERATIONS OR CRITICAL EXPERIMENTS WHEN EQUIPMENT FAILURE CAN HAVE DIRE CONSEQUENCES.

PROGRAMS RELATING TO INFORMATION DISSEMINATION AND RETRIEVAL CONTINUE TO BE OF GREAT CONCERN. THE BRANCH PROVIDES A FOCAL POINT FOR OUTSIDE MANUFACTURERS OR RESEARCH FIRMS SEEKING ENGINEERING INFORMATION FROM NIH OR OFFERING THEIR INSTRUMENTS AND ENGINEERING DEVELOPMENTS TO NIH. THIS PLACES ON THE BRANCH THE RESPONSIBILITY FOR EFFICIENT COMMUNICATION WITH ALL INTERESTED PARTIES. ORAL COMMUNICATIONS AS WELL AS MEMORANDA COVERING BRANCH PROJECTS AND OUTSIDE INSTRUMENTATION DEVELOPMENTS ARE USED TO REACH NIH SCIENTISTS; PUBLICATIONS IN PROFESSIONAL JOURNALS AND PAPERS PRESENTED AT MEDICAL AND ENGINEERING CONVENTIONS SERVE TO DISSEMINATE INFORMATION BEYOND NIH (SEE APPENDICES A AND B).

IN A NEW SCIENTIFIC DISCIPLINE SUCH AS BIOMEDICAL ENGINEERING, AWARENESS OF ITS POTENTIALITIES AMONG ENGINEERS AND SCIENTISTS--AND MORE IMPORTANT AMONG THE GENERATION OF FUTURE ENGINEERS AND SCIENTISTS NOW ATTENDING OUR UNIVERSITIES--IS NECESSARY FOR FUTURE PROGRESS. THE BRANCH USES VARIOUS MEANS TO HELP PROMOTE THIS AWARENESS: PUBLISHED ARTICLES IN PROFESSIONAL JOURNALS ON THE BIOMEDICAL ENGINEERING ACTIVITIES AT NIH; ADDRESSES AT EDUCATIONAL MEETINGS; ADVISING ON FELLOWSHIP AWARDS TO BIOMEDICAL ENGINEERING STUDENTS; PERSONAL DISCUSSIONS WITH UNIVERSITY STAFFS ON EDUCATION REQUIREMENTS AND WITH DEPARTMENT HEADS, PLACEMENT OFFICERS, AND STUDENTS ON THE HUMANE IMPORTANCE OF THE FIELD AND ITS CAREER OPPORTUNITIES.

BECAUSE OF THE CUMULATIVE YEARS OF BIOMEDICAL ENGINEERING EXPERIENCE OF ITS STAFF, THE BRANCH IS FREQUENTLY ASKED TO ASSIST OUTSIDE ORGANIZATIONS WITH ITS TECHNICAL KNOWLEDGE.

Such assistance is given freely to other Government agencies and universities. Private firms can obtain from the Branch detailed information on any previously published or patented (Appendix C) development.

Similarly, advice is sought from the Branch on methods of organizing biomedical engineering support at various universities or as regional resource centers. The Branch renders this service through personal conferences and through articles in professional journals (Appendix A) on organizational and management problems in this cross-disciplinary field. The Branch also participates in advisory panels such as the National Engineering Joint Council's Report to the President of the United States on "The National Engineering Research Needs 1965 to 1985".

Progress and Accomplishments

Summary of progress and accomplishments

Progress has been achieved in the following four main areas of Branch endeavor:

1. Major advances in engineering methods, development, and design of instrumentation as applied to medical research (described in more detail under "Significant Contributions"; the most important ones appear as individual project reports).

2. Expansion of research team participation (Branch engineers participating as members of the medical research team) into areas of biomagnetism and psycho-physiological studies.

3. Information dissemination in the biomedical engineering field.

4. Fostering cross-disciplinary biomedical engineering education.

Research team operation

In the main, the Branch operates as a centralized consulting engineering facility available to all scientists at NIH. In this manner more flexible and efficient use is made of the available engineering manpower, since a comparatively small group of engineers can serve the many hundreds of NIH life scientists. Similarly the use of tools and shop equipment--frequently highly specialized and expensive--can be scheduled in a more efficient way. There are, however, research projects at NIH whose technological complexity and importance to medical

PROGRESS ARE SUCH AS TO OVERRIDE CONSIDERATIONS OF FINANCIAL SAVING OR CONSERVATION OF MANPOWER. IN THOSE CASES THE BRANCH--ON THE INSTITUTE'S REQUEST--ASSIGNS ONE OF ITS STAFF MEMBERS FULL-TIME OR PART-TIME TO THE MEDICAL LABORATORY TO COOPERATE WITH THE LIFE SCIENTIST AS ENGINEERING MEMBER OF THE RESEARCH TEAM. THREE SUCH PROJECTS WERE ACTIVATED DURING 1962:

(1) A RESEARCH PROJECT CONDUCTED IN COOPERATION WITH NINDB ON THE EFFECTS OF HIGH INTENSITY MAGNETIC FIELDS ON BIOLOGICAL TISSUE. THE STUDY WILL COMPLEMENT A PROGRAM SIMILARLY SUPPORTED BY THIS BRANCH ON THE EFFECT OF RADIO FREQUENCY RADIATION ON TISSUE AND ANIMALS.

(2) AN INVESTIGATION BY THE CLINICAL NEUROPHARMACOLOGY RESEARCH CENTER, NIMH, INTO HUMAN MOVEMENT CONTROL BY THE CENTRAL NERVOUS SYSTEM BASED ON SENSORY FEED-BACK.

(3) IN CONJUNCTION WITH THE LABORATORY OF EXPERIMENTAL PATHOLOGY, NIAMD, A PROJECT DEALING WITH PULSED ULTRASONIC ECHO MEASUREMENTS FOR THE DETERMINATION OF THE CARTILAGE THICKNESS AND DENSITY IN NORMAL AND ARTHRITIC JOINTS.

PROGRESS ON INFORMATION DISSEMINATION

THE PROGRAM OF INFORMING NIH SCIENTISTS ON RECENT DEVELOPMENTS IN MEDICAL ENGINEERING WAS EXPANDED THIS YEAR BY ISSUING MEMORANDA COVERING DEVELOPMENTS OF OUTSIDE RESEARCH ORGANIZATIONS AND COMMERCIAL FIRMS. THESE ABSTRACTS ARE IN ADDITION TO THE ONES DESCRIBING BRANCH DEVELOPMENTS. ON A NATION-WIDE BASIS, ADDRESSES AT CONVENTIONS AND PUBLICATIONS IN PROFESSIONAL JOURNALS WERE RELIED ON TO SPREAD INFORMATION ON NEW BRANCH DEVELOPMENTS. ORAL COMMUNICATION AND GUIDED TOURS THROUGH BRANCH FACILITIES HAVE ALSO HELPED TO CARRY INFORMATION ON RECENT NIH ENGINEERING DEVELOPMENTS TO SCIENTISTS AND SURGEONS IN THIS COUNTRY AND ABROAD.

FOSTERING INTERDISCIPLINARY EDUCATION IN BIOMEDICAL ENGINEERING

THE BRANCH EFFORTS HAVE BEEN IN TWO DIRECTIONS: (1) TO PROVIDE CONTINUED ADVANCED TRAINING FOR ITS OWN STAFF IN LIFE SCIENCE SUBJECTS AND MEDICAL ENGINEERING SUBJECTS SUCH AS MIT'S COURSE ON BIOLOGICAL SERVO MECHANISMS; AND (2) TO SUPPLY INFORMATION TO UNIVERSITIES FOR USE IN ARRIVING AT TRAINING PROGRAMS FITTED TO THE NEEDS OF THE BIOMEDICAL ENGINEER. AN INCREASING NUMBER OF UNIVERSITIES ARE SHOWING INTEREST IN AND REALIZING THE NEED FOR SUCH CROSS-DISCIPLINARY TRAINING.

Significant Contributions to the NIH Research Program

A few examples of engineering developments and designs--in addition to the major projects discussed in the Individual Project Reports--will illustrate the wide range of engineering applications provided by the Branch to NIH research.

Mobile monitor for a cardiac recovery room will detect and display the patient's heart rate, electrocardiogram, and blood pressure. It actuates an alarm and makes a recording when an abnormality in any of these parameters is sensed. An automatic pacemaking system will operate in conjunction with the mobile monitor.

Skin capacitance meter to measure electrical capacitance of human skin. A small high-frequency voltage is applied to the skin through two electrodes; the current which passes is proportional to the capacitance between the two electrodes. The magnitude of the capacitance is related to the thickness of the horny layer of the skin, and thus to the thyroid gland activity. The device shows promise as a screening tool for thyroid studies.

Recording hydrophil balance to measure the kinetics of monomolecular films in a study associated with the action of certain drugs and anesthetics. The instrument uses a servomechanism to automatically maintain the surface tension of a drug film at a constant value by permitting the area occupied by the film to vary as the drug leaves the film and enters the solution below it.

Pulsed ultrasonic instrumentation for kinematic study of cartilage tissue. The need for a non-destructive method of determining the depth of cartilage over joint structures gave rise to the possibilities of using pulsed ultrasonic instrumentation. Preliminary investigations showed that the discontinuity between the bone and cartilage was detectable and that velocity of sound measurements in cartilage might give added information regarding its structure and kinematic properties. The pulsed ultrasonic system is used to make depth and velocity measurements in knee and rib cartilage, to map the cartilage and bone interface in three dimensions, and to study the relationship between the velocity of sound and the structure and density of bone and cartilage. In the instrumentation system employed, ultrasonic vibrations are generated electronically and directed as a pulsed beam through the tissues under test.

BLOOD FLOW MINIATURE PROBE. THE PROBE, USED FOR MEASURING BLOOD FLOW IN TISSUES, IS A SINGLE MICROSIZED THERMISTOR, WHICH IS HEATED BY A SMALL ELECTRIC CURRENT; CHANGES IN BLOOD FLOW PRODUCE CHANGES IN THE TEMPERATURE OF THE THERMISTOR. THESE TEMPERATURE CHANGES ARE REFLECTED AS THERMISTOR RESISTANCE CHANGES, WHICH CAN BE MEASURED AND RECORDED. THE ADVANTAGE OF THIS SYSTEM IS THAT IT ALLOWS THE USE OF VERY SMALL PROBES WHICH CAN BE PLACED IN PREVIOUSLY INACCESSIBLE REGIONS OF THE BODY.

AUTOMATIC SYRINGE DRIVE FOR PERIODIC INJECTION OF REAGENT INTO A POLAROGRAPH CELL. THE DRIVE PERIODICALLY ADVANCES A MICROMETER SYRINGE ONE TURN PER SECOND, ONCE A MINUTE. THE ERROR IS LESS THAN 0.002 TURNS AND IS NON-CUMULATIVE. THE USER MAY PRESELECT THE NUMBER OF TURNS TO BE MADE UP TO 400. RELAY CONTACTS SHUT OFF THE MACHINE WHEN THE PRESET NUMBER IS REACHED. SIMPLE ADJUSTMENTS PERMIT CYCLE TIMES OF MORE OR LESS THAN ONE MINUTE AS WELL AS MULTIPLE REVOLUTIONS PER CYCLE (AT THE RATE OF ONE REVOLUTION PER SECOND). THE AUTOMATIC SYRINGE DRIVE PERFORMS UNATTENDED THROUGH A LARGE NUMBER OF INJECTIONS, WITH HIGH ACCURACY. THE TIMING PROGRAM OF PERIODIC INJECTION ALLOWS ESTABLISHMENT OF EQUILIBRIUM AFTER EACH INJECTION.

SLOPE DETECTOR AND TIME DISPLAY FOR ELECTRICAL RESPONSE CURVES. THE ELECTRONIC DEVICE AUTOMATICALLY DETECTS AND DISPLAYS THE TIME INTERVAL BETWEEN THE BEGINNING AND THE PEAK OF A MUSCLE RESPONSE CURVE. THE DEVICE DETECTS THE PRESENCE OF A SLOPE TO THE CURVE AND COMMENCES TO COUNT TIME UNTIL THE CURVE REACHES ITS PEAK AMPLITUDE. THE TIME COUNT IS DISPLAYED--TOGETHER WITH THE CURVE--ON AN OSCILLOSCOPE IN THE FORM OF 1 MILLISECOND PIPS ARRANGED IN GROUPS OF TEN FOR EASY READABILITY. THIS TYPE OF DETECTION AND DISPLAY PROVIDES A STANDARD FOR MEASUREMENT AND COMPARISON OF CURVES. IT PRESENTS A CONVENIENT MEANS OF PLACING THE INFORMATION DIRECTLY ON A PHOTOGRAPHIC RECORDING. THE SAME INSTRUMENTATION CAN BE USED WITH ANY TYPE OF CURVE RESPONSE OF A SIMILAR NATURE, I.E., WITH ANY CURVE HAVING A CONTINUOUS POSITIVE SLOPE FROM BEGINNING TO PEAK.

ANCILLARY CIRCULATION BOOSTER FOR CEREBRAL HYPOTHERMIA. A BLOOD FLOW BYPASS SYSTEM FOR CEREBRAL COOLING IN WHICH NO EXTERNAL OXYGENATION WILL OCCUR AT BLOOD TEMPERATURES ABOVE 25°C, AND FULL OXYGENATION OCCURS AT TEMPERATURES BELOW 25°C. ABOVE 25°C, THE SYSTEM REMOVES BLOOD FROM THE FEMORAL ARTERY, COOLS AND RETURNS IT TO THE FEMORAL VEIN. BELOW 25°C, THE FLOW IS REVERSED AND BLOOD IS REMOVED FROM THE INFERIOR VENA CAVA BY CATHETERIZATION, PASSED THROUGH THE ANCILLARY CIRCULATION BOOSTER, OXYGENATED, AND RETURNED TO THE PATIENT'S ARTERIAL SYSTEM. THE ENTIRE EXTRACORPOREAL FLOW SYSTEM IS ENCASED IN A STERILE ATMOSPHERE AND IS DESIGNED TO BE ASSEMBLED FROM PREPACKAGED, DISPOSABLE, STERILIZED CONNECTING TUBING. SAMPLE WITHDRAWAL AND INTRAVENOUS BAG PRIMING OF THE SYSTEM ARE TO BE

ACCOMPLISHED BY SINGLE USE STERILIZED ENTRANCES. THE UNIT IS THE FIRST--TO OUR KNOWLEDGE--THAT PERMITS FLOW REVERSAL IN THE EXTRACORPOREAL CIRCUIT TO ASSIST THE HEART IN CIRCULATING MORE VISCOUS BLOOD.

A CONDUCTIVE ELASTOMER WHICH COMBINES HIGH ELECTRIC CONDUCTIVITY WITH THE RESILIENT PROPERTIES OF AN ELASTOMER. THE PLASTIC MATERIAL WAS DEVELOPED BY INCORPORATING FINELY DIVIDED SILVER DUST OF 1/4 TO 2μ PARTICLE SIZE INTO A LOW VISCOSITY FLEXIBLE VINYL PLASTISOL IN APPROPRIATE PROPORTIONS AND UNDER REGULATED TEMPERATURE AND PRESSURE CONDITIONS. THE IMMEDIATE AIM OF THE DEVELOPMENT WAS TO PROVIDE ELECTRODES IN CONTACT WITH THE EYEBALL FOR USE WITH ELECTRORETINOGRAPHS. THE ELECTRICALLY CONDUCTIVE MATERIAL CAN BE FORMED INTO THE SHAPE OF A MEMBRANE IN CONTACT WITH THE CORNEA, AND IS FLEXIBLE ENOUGH TO FOLLOW THE MOVEMENTS OF THE EYEBALL WITHOUT INTERFERING WITH ELECTRICAL SIGNAL DETECTION.

A BLOOD LOSS MEASUREMENT SYSTEM WHICH PERMITS THE GRAVIMETRIC MEASUREMENT OF BLOOD LOST DURING CARDIAC SURGERY. A CONTAINER IN THE SUCTION LINE, SUSPENDED FROM A FORCE TRANSDUCER, COLLECTS THE BLOOD FROM THE OPEN CHEST. THE ELECTRICAL SIGNALS FROM THE FORCE TRANSDUCER ARE DISPLAYED ON A LARGE METER. THE CAPACITY OF THE SYSTEM IS 4 LITERS AND MEASUREMENTS ARE MADE WITH AN ACCURACY OF ± 20 MILLILITERS.

MICROMANIPULATOR FOR DEPTH ELECTRODES USED IN BRAIN STUDIES ON UNANESTHETIZED ANIMALS. A LIGHT-WEIGHT, SELF-POWERED UNIT, SMALL ENOUGH TO BE USED ON THE HEAD OF A SMALL ANIMAL, THE MICRODRIVE HAS THE FOLLOWING DESIRABLE FEATURES: IT HAS A REPRODUCIBLE ACCURACY OF ONE-HALF MICRON WITHOUT OVERDRIVE OR BACKLASH, AND IT CAN BE OPERATED BY SIMPLE REMOTE SWITCHING WHICH REQUIRES NO SPECIAL SKILL OF THE OPERATOR. FURTHER DEVELOPMENT IS UNDERWAY FOR ADAPTING THE DRIVE PRINCIPLE TO DOUBLE MICRODRIVES. BECAUSE OF THE SIMPLICITY OF THE SETTING DEVICE, AUTOMATIC FEEDBACK CONTROL OF THE DEPTH ELECTRODE PENETRATION INTO THE TISSUE IS ALSO CONSIDERED AS A FUTURE POSSIBILITY. THE SMALL SIZE AND SIMPLICITY OF THE DEVICE MIGHT EVENTUALLY MAKE POSSIBLE THE SIMULTANEOUS RECORDING OF ELECTRIC ACTIVITY FROM SEVERAL BRAIN NEURONS.

CORTICAL COOLING SYSTEM. A SYSTEM FOR SPOT AND AREA COOLING OF THE CORTEX TO IMPROVE THE SURGICAL TECHNIQUE FOR REMOVING ABNORMALITIES. IT IS HOPED THAT SUCH A DEVELOPMENT WOULD REDUCE OR ELIMINATE THE NEED OF ELECTROCAUTERIZING THE SURGICALLY SEVERED BLOOD VESSELS, AND THUS PREVENT ADDITIONAL CORTICAL DESTRUCTION. THE APPARATUS IN ITS PRESENT STATE OF DEVELOPMENT CONSISTS OF A STAINLESS STEEL CYLINDER PARTIALLY ENCASED BY A DISPOSABLE LATEX RUBBER DIAPHRAGM WHICH HAS PREVIOUSLY BEEN FILLED WITH A STERILE STARCH GLYCEROL-WATER SOLUTION. THE DIAPHRAGM IS PLACED IN CONTACT WITH THE CORTEX,

AND ASSUMES THE SAME CONTOUR AS THE EXPOSED SURFACE. COOLING OCCURS BY THE EXPANSION OF REFRIGERATED AIR IN THE CYLINDER CHAMBER, WHICH IN TURN COOLS THE LIQUID IN CONTACT WITH THE CYLINDER. THE CORTEX IS COOLED BY THE TRANSFER OF HEAT THROUGH THE LATEX MEMBRANE INTO THE STARCH GLYCEROL-WATER SOLUTION. RATE OF COOLING IS CONTROLLED BY THE VOLUME PER UNIT TIME OF REFRIGERATED AIR FLOWING INTO THE CYLINDER.

A HIGH PRESSURE BACTERIA FILTER FOR SEGREGATING POPULATIONS OF E. COLI. BACTERIA BY SIZE USES AIR PRESSURE TO FORCE FIVE LITERS OF SOLUTION CONTAINING THE BACTERIA THROUGH A SERIES OF POROUS METAL FILTERS AND FILTER PAPERS. THE FILTRATION CAN TAKE PLACE IN A MATTER OF SECONDS, DEPENDING ON THE POROSITY OF THE FILTER SERIES USED, AND RESULTS IN A SYNCHRONOUSLY DIVIDING POPULATION BASED UPON SIZE SELECTION. IT IS DESIGNED TO SAFELY WITHSTAND AN AIR PRESSURE OF 120 PSI.

THERAPEUTIC MATTRESS. THE MATTRESS, CONSISTING OF A HERMETICALLY SEALED PLASTIC COVER AND PLASTIC INTERIOR STIFFENERS, IS FILLED WITH WATER WHOSE TEMPERATURE CAN BE ADJUSTED FOR MAXIMUM PATIENT COMFORT. THE WATER SUPPLY SYSTEM IS CONNECTED THROUGH SEALED-IN WATER INTAKE AND OUTLET, AND CONTROLS INTERIOR WATER FLOW, WATER PRESSURE, AND WATER TEMPERATURE. THE MATTRESS SUPPORTS THE PATIENT IN A FLOATING POSITION DURING OR AFTER SURGERY, FOLLOWING THE CONTOURS OF THE PATIENT'S BODY. PLANS CALL FOR INITIAL USE IN NEUROLOGICAL SURGERY.

TWO-WAVELENGTH MICROCOLORIMETER TO PERMIT STUDY OF THE REACTION RATE OF VERY SMALL AMOUNTS OF CILIARY BODY CARBONIC ANHYDRASE ENZYME. CARBONIC ANHYDRASE IS ASSOCIATED WITH THE PRODUCTION OF INTRAOCULAR FLUID, THE OVERPRODUCTION OF WHICH MAY BE A CAUSE OF GLAUCOMA. LIGHT TRANSMISSION OF A pH SENSITIVE DYE IS MEASURED AT TWO WAVELENGTHS. AS THE ENZYME CONSUMES ITS SUBSTRATE, THE pH CHANGES, AND THE DYE CHANGES COLOR. THE TIME REQUIRED FOR THE pH TO CHANGE A PRESCRIBED AMOUNT IS PROPORTIONAL TO THE ENZYME ACTIVITY.

INSTRUMENTATION FOR THE NEW CARDIAC, NEUROLOGY, AND CARDIOLOGY OPERATING ROOMS. ITS SALIENT FEATURES ARE: THE COLLECTION OF ALL MONITORING, RECORDING, AND SERVICE EQUIPMENT INTO A CONSOLE IN A CENTRAL RECORDING ROOM; A DISPLAY IN THE OPERATING ROOM OF THE PULSE, ELECTROCARDIOGRAM AND ELECTROENCEPHALOGRAM WAVEFORMS, AND A DIGITAL PRESENTATION IN THE OPERATING ROOM OF HEART RATE, BLOOD PRESSURE, BLOOD FLOW, ETC.

CHANGES AND IMPROVEMENTS

IN CARRYING OUT ITS FUNCTIONS, THE BRANCH ENDEAVORS TO MAINTAIN AND IMPROVE CLIENT SATISFACTION AND EFFICIENCY OF OPERATION.

SERVICE WAS IMPROVED BY THE ESTABLISHMENT OF TWO NEW BRANCH AREA SHOPS FOR GEOGRAPHICALLY CLOSE COOPERATION BETWEEN THE

BRANCH'S FABRICATION AND REPAIR PERSONNEL AND THE LABORATORIES THEY SERVE ON THE MANY MINOR JOB REQUESTS TOO SMALL TO WARRANT TRANSMITTAL TO THE CENTRAL SHOP FACILITIES.

AS TO EFFICIENCY, THE BRANCH HAS SHOWN IMPROVEMENT DURING THE LAST YEAR AS A RESULT OF ITS CONTINUOUS STREAMLINING EFFORTS. THE INDIRECT COST OF PRODUCTION (OVERHEAD) HAS BEEN REDUCED. THE IMPROVEMENT IN EFFICIENCY CAN BE ATTRIBUTED MAINLY TO THREE OPERATIONAL CHANGES:

(1) INTRODUCTION OF MACHINE COMPUTATION OF TIME AND MATERIAL COSTS. THIS HAS FREED SUPERVISORY PERSONNEL OF MUCH PAPERWORK AND HAS THUS IMPROVED THE OUTPUT VOLUME AND QUALITY OF THEIR UNITS.

(2) MODERNIZATION OF SHOP EQUIPMENT AND MACHINE TOOLS. WORN AND OBSOLETE MACHINERY HAS BEEN REPLACED WITH NEW AND MORE EFFICIENT EQUIPMENT. THIS IS PART OF A CONTINUED PROGRAM OF THE BRANCH.

(3) INCREASE IN STAFF OF QUALIFIED ENGINEERS. THE BRANCH CAN NOW OFFER IMPROVED ENGINEERING SUPPORT TO ITS FABRICATION PERSONNEL IN MORE DIFFICULT AND COMPLEX CASES OF FABRICATION, REPAIR, AND MAINTENANCE.

PROBLEMS

THE TWO MAIN PROBLEMS OF THE BRANCH CONTINUE TO BE INADEQUATE SPACE AND INADEQUATE STAFFING. IT IS HOPED THAT ADDITIONAL WORK SPACE WILL BECOME AVAILABLE SOON, SINCE THE PRESENT AREA WILL NOT ALLOW MEETING THE INCREASED STAFF AND EQUIPMENT DEMANDS EXPECTED FOR 1963.

THE MAIN SHORTAGE OF PERSONNEL EXISTS IN THE ENGINEERING SECTIONS. IT IS CAUSED BY THE INCREASING NUMBER OF RESEARCH INVESTIGATORS AT NIH IN NEED OF ENGINEERING SUPPORT, AND BY THE CRITICALLY SHORT SUPPLY OF QUALIFIED ENGINEERS--PARTICULARLY IN THE BIOMEDICAL ENGINEERING FIELD.

FUTURE OBJECTIVES

THE BRANCH WILL CONTINUE TO STRIVE FOR HIGH-QUALITY SERVICE TO THE NIH INTRAMURAL RESEARCH PROGRAM AND FOR EFFECTIVE COOPERATION WITH BIOMEDICAL ENGINEERING ACTIVITIES OUTSIDE NIH. THE BUILDING-UP OF EXPERT KNOWLEDGE IN NEWLY-DEVELOPING DISCIPLINES OF ENGINEERING AS APPLIED TO MEDICAL RESEARCH

(SUCH AS SOLID STATE DEVICES AND BIOMAGNETISM) WILL BE OF MAIN CONCERN. THE BRANCH PROGRAM OF IMPROVED FAILURE DIAGNOSES AND PREVENTIVE MAINTENANCE WILL BE STRENGTHENED THROUGH ADDED ENGINEERING SUPPORT. PLANS ARE ALSO UNDERWAY FOR A THOROUGH REVIEW OF NEEDS AND METHODS OF BETTER OPERATION AND UTILIZATION OF SCIENTIFIC INSTRUMENTS AND INSTRUMENTATION SYSTEMS AT NIH.

Appendix A

Publications:

Alt, F.: Biomedical instrument engineering at the National Institutes of Health. American Journal of Medical Electronics 1: 87-91, No. 2, 1962.

Riggle, G. C., and De Broske, J. M. F.: Recent advances in heart-lung bypass systems. Communication and Electronics No. 60, 62-63, 1962.

Alt, F.: Management responsibilities in biomedical engineering. Bio-Medical Purview 2: 31-35, 1962.

Appendix B

Presentations:

Cohen, G. S.: Survey on recent technical developments at NIH in the field of neurosurgery with emphasis on instrumentation system for neurosurgical operating suites. Meeting of Scientific Councilors of the National Institute of Neurological Diseases and Blindness. February 1962.

Elmore, S., Sokoloff, L., Carmeci, P., and Norris, G.: The nature of imperfect elasticity of articular cartilage. Annual meeting of the American Rheumatism Association. Chicago, Illinois, June 1962. (Also accepted for publication by the Journal of Applied Physiology.)

Chase, R. A., and Cullen, J. K.: Experimental studies on motor control systems in man. 12th Annual Symposium on Recent Developments in Research Methods and Instrumentation. Bethesda, Maryland, October 1962.

Chase, R. A., and Cullen, J. K.: Human movement control by the central nervous system based on sensory feedback. Informal seminar presentations. Albert Einstein Medical School, New York, October 1962; and Haskins Laboratory, New York, October 1962.

Appendix C

Patent Suggestions:

January 1962--Therapeutic Mattress, Laurence R. Crisp

January 1962--Conductive Elastomer, John W. Boretos

July 1962--Implantable Cortical Electrodes, John W. Boretos and Gerald S. Cohen

August 1962--Disposable Fluid Withdrawal and Injection Manifold for Heart-Lung Machines, Grant C. Riggle

October 1962--Thermoscope, William Pearlman

(ATTACHMENT 1)

SERIAL NO. 8.1
1. INSTRUMENT ENGINEERING AND DEVELOPMENT BRANCH
2. INSTRUMENT FABRICATION SECTION, ENGINEERING DEVELOPMENT SECTION
3. BETHESDA, MARYLAND

PHS-NIH
INDIVIDUAL PROJECT REPORT
CALENDAR YEAR 1962

PART A.

PROJECT TITLE: MULTI-TERMINAL CORTICAL ELECTRODE FOR CHRONIC IMPLANT

PRINCIPAL INVESTIGATORS: JOHN W. BORETOS, PAUL T. CALDERWOOD, GERALD S. COHEN

COOPERATING UNIT: NATIONAL INSTITUTE OF NEUROLOGICAL DISEASES AND BLINDNESS, SURGICAL NEUROLOGY BRANCH

MAN YEARS (CALENDAR YEAR 1962):
TOTAL: 0.8
PROFESSIONAL: 0.3
OTHER: 0.5

PROJECT DESCRIPTION:

OBJECTIVE. TO FURNISH THE NEUROSURGEON WITH A MEANS FOR ELECTRICALLY EXPLORING LARGE AREAS OF THE CORTICAL SURFACE. AT PRESENT USED ONLY DURING NEUROSURGICAL PROCEDURES, IT IS INTENDED THAT THE ELECTRODE SHOULD BE CHRONICALLY IMPLANTABLE FOR POST-OPERATIONAL NEUROLOGICAL STUDIES OVER EXTENDED PERIODS.

THE NEW ELECTRODE DEVICE CONSISTS OF A FINE SHEET OF TRANSPARENT PLASTIC ONLY 1/4 MIL (.00025 INCH) THICK ONTO WHICH ARE ETCHED 36 ELECTRODE TERMINAL POINTS AND THEIR CONNECTING WIRES. DUE TO THE THINNESS OF THE PLASTIC SHEET, IT CLINGS TIGHTLY TO THE SURFACE OF THE EXPOSED BRAIN, ASSURING GOOD ELECTRICAL CONTACT AT THE MANY ELECTRODE POINTS. AFTER THE PLASTIC SHEET IS PLACED ON THE BRAIN SURFACE, REPOSITIONING IS UNNECESSARY SINCE THE LARGE NUMBER OF CLOSELY SPACED (1 CM) ELECTRODES CAN BE EXPLORED BY SELECTOR SWITCHES ON THE EEG RECORDER.

UNIQUE TECHNIQUES WERE DEVELOPED TO ETCH THE ELECTRODE POINTS AND CONNECTING WIRING ONTO THE PLASTIC SHEET SIMILAR TO PRINTED CIRCUITRY, AND TO SOLDER THE PRINTED CONDUCTORS TO THE WIRES IN THE LEAD CABLE. THE SELECTOR SWITCHING ARRANGEMENT IS CONTAINED IN A SEPARATE ELECTRICAL CONTROL BOX WITH COLOR CODED TERMINALS.

SIGNIFICANCE TO BIOMEDICAL RESEARCH. THE IMPLANT PERMITS--TO THE DEVELOPERS' KNOWLEDGE FOR THE FIRST TIME--AN EVALUATION OF SIGNALS FROM A COMPARATIVELY LARGE AREA OF THE CORTEX OVER AN EXTENDED PERIOD OF TIME. PREVIOUS TECHNIQUES FOR MAKING CORTICAL RECORDINGS DURING A NEUROSURGICAL PROCEDURE EMPLOYED ELECTRODES ATTACHED TO LENGTHS OF FLEXIBLE METAL WIRE. EACH ELECTRODE HAD TO BE PLACED WITH EXTREME CARE TO AVOID SHORTING AND TO MAINTAIN GOOD CONTACT. IN ORDER TO ELECTRICALLY EXPLORE AN ADJACENT CORTICAL AREA, IT WAS NECESSARY TO REPEAT THE LABORIOUS AND TIME-CONSUMING ELECTRODE-POSITIONING PROCEDURE. USED AT PRESENT IN EPILEPSY RESEARCH FOR LOCATING THE EPILEPTIC FOCUS, DIRECT APPLICATION IS EXPECTED TO OTHER NEUROSURGICAL STUDIES.

IN ITS PRESENT EARLY STAGES OF USE, THE ELECTRODES HAVE BEEN IMPLANTED IN A PATIENT FOR A PERIOD OF ONE WEEK. FUTURE DEVELOPMENT AS CHRONICALLY IMPLANTABLE ELECTRODES IS EXPECTED.

PART B INCLUDED: NO

(Attachment 1)

Serial No. 8.2
1. Instrument Engineering and Development Branch
2. Electronic Engineering Section
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A.

Project Title: Experimental Analysis of the Motor Control Systems in Man

Principal Investigators: Richard A. Chase and John K. Cullen

Other Investigators: Joseph Openshaw and Robert Byck

Cooperating Unit: National Institutes of Mental Health, Clinical Neuropharmacology Research Center (their serial no. M-NC (S.E.)-OC-7)

Man Years (this Branch, calendar year 1962):
Total: 0.6
Professional: 0.5
Other: 0.1

Project Description:

Objective. To study the utilization of sensory feedback information in the control of voluntary motor activity in the normal nervous system of man. To study the utilization of sensory feedback information in the control of voluntary motor activity in patients who have diseases of the nervous system characterized by abnormal movements.

Methods Employed. The input-output relationships of the motor control system associated with the movement of the index finger are studied by providing the subject with a compensatory tracking task in which the form of the error signal may be controlled. Constant input is provided by establishing a fixed reference point in space and representing its position by means of a fixed trace at the midpoint of a dual beam oscilloscope screen. The second

TRACE IS THEN UTILIZED TO DISPLAY AN ANALOG SIGNAL RELATED TO THE POSITION OF THE INDEX FINGER IN SPACE. A PULLEY SYSTEM AND ROTARY POTENTIOMETER ARE USED TO PROVIDE AN ELECTRICAL SIGNAL PROPORTIONAL TO THE MOVEMENT OF THE INDEX FINGER WITH RESPECT TO THE FIXED REFERENCE POSITION. THIS ELECTRICAL REPRESENTATION OF THE FINGER MOTION MAY THEN BE TRANSFORMED BY AMPLIFICATION, INTEGRATION, DIFFERENTIATION, OR BY TAKING ITS LOGARITHM TO THE BASE 2. A THRESHOLD CRITERION MAY BE APPLIED, THUS DEFINING THE ORDER OF MAGNITUDE OF FINGER MOVEMENT NECESSARY TO PROVIDE A VISUAL ERROR SIGNAL. ADDITIONALLY, THE ERROR SIGNAL MAY BE PRESENTED AS AN INTERMITTENT PULSE OF INFORMATION WITH VARIABLE ON AND OFF TIMES OVER THE RANGE OF 1 TO 1,000 MILLISECONDS.

THE PATTERN OF FINGER MOTION RELATED TO A PARTICULAR VISUAL DISPLAY IS RECORDED ON A HEAT RECTILINEAR POLYGRAPH. TWO CHANNELS OF REDUCED DATA ARE ALSO RECORDED. THE FREQUENCY ABOUT THE REFERENCE POINT IS MEASURED AS WELL AS THE TOTAL ERROR DURING A FIXED SAMPLE PERIOD.

SIGNIFICANCE TO BIOMEDICAL RESEARCH. THE DEFINITION OF THE RELATIONSHIP OF VISUALLY PRESENTED FEEDBACK TO THE PARTICULAR MOTOR OUTPUT WILL PROVIDE INFORMATION ABOUT THE SENSORY FEEDBACK REQUIREMENTS FOR THE CONTROL OF MOTOR ACTIVITY IN MAN. IN ADDITION, EXPERIMENTAL FINDINGS FROM THIS STUDY ARE ALSO PERTINENT TO THE DEFINITION OF COMPLEX INFORMATION PROCESSING FUNCTIONS OF THE CENTRAL NERVOUS SYSTEM. THE STUDY OF ABNORMALITIES OF MOTOR CONTROL MAY YIELD INFORMATION CONCERNING ABNORMALITIES OF COMPLEX PROCESSING AS WELL AS PROVIDING A MORE QUANTITATIVE EXPRESSION OF THE TYPE AND EXTENT OF MOTOR DEFICIT. THE INSTRUMENTATION DEVELOPED FOR THIS STUDY PROVIDES THE FRAMEWORK FOR ADVANCEMENT IN QUANTITATIVE MEASUREMENT OF PHYSIOLOGICAL EVENTS IN MAN. THE METHODS AND TECHNIQUES DEVELOPED WITHIN THIS LABORATORY MAY BE CLINICALLY APPLICABLE TO THE ACCURATE DIAGNOSIS OF COMPLEX NEUROLOGICAL DISORDERS.

PART B INCLUDED: YES

(Attachment 1)

Serial No. 8.2

PHS-NIH
Individual Project Report
Calendar Year 1962

Part B. Honors, Awards, and Publications

Publications other than abstracts from this project:

Chase, R. A., and Cullen, J. K.:
Experimental studies on motor control systems in man. Paper read at the Symposium on Recent Developments in Research Methods and Instrumentation. National Institutes of Health, Bethesda, Maryland. October 1962.

(ATTACHMENT 1)

SERIAL NO. 8.3
1. INSTRUMENT ENGINEERING AND DEVELOPMENT BRANCH
2. ENGINEERING DEVELOPMENT SECTION, MECHANICAL ENGINEERING SECTION
3. BETHESDA, MARYLAND

PHS-NIH
INDIVIDUAL PROJECT REPORT
CALENDAR YEAR 1962

PART A.

PROJECT TITLE: CARTILAGE COMPRESSOMETER

PRINCIPAL INVESTIGATORS: PETER CARMECI AND GEORGE F. NORRIS

COOPERATING UNIT: NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, LABORATORY OF EXPERIMENTAL PATHOLOGY (THEIR SERIAL NO. NIAMD-LEP-14)

MAN YEARS (CALENDAR YEAR 1962):
TOTAL: 0.2
PROFESSIONAL: 0.2
OTHER: -

PROJECT DESCRIPTION:

OBJECTIVE. TO DEVISE AN INSTRUMENTATION METHOD FOR THE STUDY OF ELASTIC PROPERTIES OF CARTILAGE.

METHODS EMPLOYED. A LEVER SYSTEM EXERTS FORCES TO SMALL AREAS OF CARTILAGE SURFACE. VARIOUS TRANSDUCER ELEMENTS SENSE THE PRESSURES AND DEFORMATIONS RESULTING IN THE CARTILAGE AS WELL AS THE RESIDUAL INDENTATION AFTER THE FORCE IS REMOVED. ALL DATA ARE AUTOMATICALLY RECORDED AS FUNCTIONS OF TIME. THE INSTRUMENTS PERMIT REPRODUCIBLE MEASUREMENT OF COMPRESSION DEFORMATION OF AS LITTLE AS 10 MICRONS. THE SYSTEM CAN OPERATE IN AIR OR IMMERSED IN FLUID. SOLUTIONS OF DIFFERENT ACIDITY, TEMPERATURE, AND IONIC CONCENTRATION ARE USED.

SIGNIFICANCE TO BIOMEDICAL RESEARCH. THE CARTILAGE COMPRESSOMETER AS USED IN THE STUDY OF ARTICULAR CARTILAGE PROVIDES A NEW APPROACH TO RESEARCH ON THE CAUSE OF JOINT DISEASES SUCH AS OSTEOARTHRITIS. ITS USE UNDER IMMERSION CONDITIONS ALLOWS CLOSE SIMULATION OF THE NATURAL IN VIVO ENVIRONMENT OF THE JOINT UNDER STUDY.

PART B INCLUDED: YES

(Attachment 1)

Serial No. 8.3

PHS-NIH
Individual Project Report
Calendar Year 1962

Part B. Honors, Awards, and Publications

Publications other than abstracts from this project:

Elmore, S., Sokoloff, L., Carmeci, P., and Norris, G.: The nature of imperfect elasticity of articular cartilage. Accepted for publication in the Journal of Applied Physiology.

(Attachment 1)

Serial No. 8.4
1. Instrument Engineering and Development Branch
2. Instrument Fabrication Section
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1962

Part A.

Project Title: Neurosurgical Depth Electrode for Stimulation and Lesion-Making

Principal Investigators: Kenneth T. Bolen and Sherman D. Oxendine

Cooperating Unit: National Institutes of Neurological Diseases and Blindness, Surgical Neurology Branch

Man Years (calendar year 1962):
Total: 0.2
Professional: -
Other: 0.2

Project Description:

Objective. To combine into one neurosurgical instrument the two previously distinct functions of a device for making radio frequency brain lesions and a stimulating and recording depth electrode.

Methods Employed. Six fine stainless steel wires lead to the stimulating and recording contacts of a depth electrode. An additional 30-gauge pure silver wire serves the lesion maker. All seven wires are coated for insulation and arranged in a thin, long, polyethylene tube of less than 5/100 inch outside diameter which forms the main body of the instrument. The six stimulating and recording contacts are distributed over the 5 cm active portion of the electrode at various spacings from 2 to 10 mm, with the lesion-making contact at the electrode tip. The lesion-making device consists of an 8 mm hollow cylindrical silver probe. At the other end the electrode terminates in a small seven-pin connector of special IEDB design.

Significance to Biomedical Research. Used in the treatment of Parkinson's disease, the instrument represents a significant improvement in the field of neurosurgical depth electrodes; it eliminates the surgical procedure that was formerly necessary to remove the stimulating electrode and insert a separate lesion-making probe. The lesion-making depth electrode is inserted into the brain and the desired site for the lesion is determined through the use of the stimulating contacts. The electrode is then withdrawn slightly until the silver tip is at the selected site and the lesion can be made.

Part B included: No

(ATTACHMENT 1)

SERIAL NO. 8.5
1. INSTRUMENT ENGINEERING AND DEVELOPMENT BRANCH
2. ELECTRONIC ENGINEERING SECTION, INSTRUMENT FABRICATION SECTION
3. BETHESDA, MARYLAND

PHS-NIH
INDIVIDUAL PROJECT REPORT
CALENDAR YEAR 1962

PART A.

PROJECT TITLE: REVERSIBLE PLANAR BRAIN COOLING

PRINCIPAL INVESTIGATORS: ROBERT BYCK, JOHN K.CULLEN, PAUL P. DIRLIK

COOPERATING UNITS: NATIONAL INSTITUTE OF MENTAL HEALTH, CLINICAL NEUROPHARMACOLOGY RESEARCH CENTER

MAN YEARS (CALENDAR YEAR 1962):
TOTAL: 0.3
PROFESSIONAL: 0.1
OTHER: 0.2

PROJECT DESCRIPTION:

OBJECTIVE. TO STUDY THE USE OF REFRIGERATION IN THE CREATION OF REVERSIBLE LESIONS WITHIN THE CENTRAL NERVOUS SYSTEM OF ANIMALS.

METHODS EMPLOYED. A COUNTER-CURRENT HEAT EXCHANGE DEVICE HAS BEEN DEVELOPED FOR CHRONIC IMPLANTATION IN THE BRAIN OF CATS. THIS HEAT EXCHANGER CONSISTS OF A FORK OR PICKET FENCE ARRANGEMENT OF THERMODES PROVIDED WITH INLET AND OUTLET MANIFOLDS FOR THE CIRCULATION OF A REFRIGERANT. THE REFRIGERANT, N-HEPTANE, IS PASSED THROUGH THE FORK FROM A STAINLESS STEEL HEAT EXCHANGE COIL IN A DRY ICE-ETHANOL BATH BY A SPECIALLY DESIGNED POSITIVE DISPLACEMENT PUMP. TEMPERATURE MEASUREMENTS ARE MADE WITH CUSTOM-MADE MINIATURE THERMISTOR PROBES THROUGHOUT THE THERMODYNAMIC SYSTEM.

Significance to Biomedical Research. The development of techniques and devices for reversible ablation of areas of the central and peripheral nervous system will provide a powerful means for establishing anatomical and functional correlates. The application of refrigeration in this study will lead to a clearer understanding and definition of the thermodynamic properties of living nervous tissue.

Part B included: No

(ATTACHMENT 1)

SERIAL NO. 8.6
1. INSTRUMENT ENGINEERING AND DEVELOPMENT BRANCH
2. MECHANICAL ENGINEERING SECTION, ELECTRONIC ENGINEERING SECTION
3. BETHESDA, MARYLAND

PHS-NIH
INDIVIDUAL PROJECT REPORT
CALENDAR YEAR 1962

PART A.

PROJECT TITLE: AUTOMATIC PIPETTING APPARATUS

PRINCIPAL INVESTIGATORS: GEORGE F. NORRIS AND GRANT C. RIGGLE

COOPERATING UNIT: DIVISION OF BIOLOGICS STANDARDS, LABORATORY OF VIROLOGY AND RICKETTSIOLOGY

MAN YEARS (CALENDAR YEAR 1962):
TOTAL: 0.6
PROFESSIONAL: 0.4
OTHER: 0.2

PROJECT DESCRIPTION:

OBJECTIVE. TO PROVIDE A MEANS OF AUTOMATICALLY ASPIRATING AND DISCHARGING FLUIDS FROM PIPETTES WITH A HIGH DEGREE OF REPEATABLE ACCURACY AND A FAST RATE OF SPEED, AND WITHOUT THE HAZARDS OF MOUTH ASPIRATION.

METHODS EMPLOYED. A PISTON MOVING IN A TUBE RUBBER-SEALED TO THE PIPETTE CREATES A VACUUM FOR ASPIRATION OR DISPLACEMENT FOR DISCHARGE. THE FINAL PISTON POSITION IS OBTAINED BY PHOTOELECTRICALLY CONTROLLING THE ROTATION ANGLE OF THE DRIVE MOTOR: A SLOTTED DISK ROTATES WITH THE MOTOR; A PRESET COUNTER MECHANISM AND A PHOTOELECTRIC POSITION SENSING DEVICE CONTROLS THE ANGLE OF MOTOR ROTATION AND THUS THE FLUID VOLUME METERED. THE NUMBER OF TIMES THESE AMOUNTS ARE TO BE METERED CAN BE PROGRAMMED IN THE SAME MANNER. THE QUANTITY ASPIRATED MAY BE DISCHARGED IN UP TO TEN INSTALLMENTS OF PRESELECTABLE VOLUME. THE SYSTEM CAN ASPIRATE AND DISCHARGE FROM 10 AND 2 CC PIPETTES MAINTAINING REPEATABLE ACCURACIES DOWN TO 1/2%. IT AVOIDS LARGE PRESSURES AND VELOCITIES THAT MIGHT CAUSE VAPORIZATION OR SPLASH.

Significance to Biomedical Research. The apparatus eliminates the need for pipetting by mouth and thus improves safety when applied to toxic or pathogenic liquids. It also provides the researcher with a highly accurate and repeatable means of pipetting that can be operated quickly and readily by inexperienced personnel.

Part B included: No

(ATTACHMENT 1)

SERIAL NO. 8.7
1. INSTRUMENT ENGINEERING AND DEVELOPMENT BRANCH
2. ENGINEERING DEVELOPMENT SECTION
3. BETHESDA, MARYLAND

PHS-NIH
INDIVIDUAL PROJECT REPORT
CALENDAR YEAR 1962

PART A.

PROJECT TITLE: CONSTANT CURRENT CORTICAL STIMULATOR

PRINCIPAL INVESTIGATOR: GERALD S. COHEN

COOPERATING UNIT: NATIONAL INSTITUTE OF NEUROLOGICAL DISEASES AND BLINDNESS, SURGICAL NEUROLOGY BRANCH

MAN YEARS (CALENDAR YEAR 1962):
TOTAL: 0.2
PROFESSIONAL: 0.1
OTHER: 0.1

PROJECT DESCRIPTION:

OBJECTIVE. TO FACILITATE THE ESTABLISHMENT AND MAINTENANCE OF STIMULUS THRESHOLD DURING BRAIN-MAPPING PROCEDURES BY COMPENSATING FOR VARIATIONS IN CONTACT AND TISSUE RESISTANCE.

METHODS EMPLOYED. THE CONSTANT CURRENT STIMULATOR DELIVERS A PREDETERMINED CURRENT TO A PREPARATION FAIRLY INDEPENDENT OF THE RESISTANCE IN THE EXTERNAL CIRCUIT. THE STIMULATOR DELIVERS 2.5 MILLISECOND PULSES AT A 60 CPS REPETITION RATE AND A CONSTANT CURRENT OF UP TO 2 MILLIAMPERES, WHILE THE TOTAL EXTERNAL CIRCUIT RESISTANCE MAY VARY BETWEEN 0 AND 10,000 OHMS.

SIGNIFICANCE TO BIOMEDICAL RESEARCH. A CONSTANT CURRENT STIMULATOR OFFERS SEVERAL ADVANTAGES OVER THE CONSTANT VOLTAGE STIMULATORS GENERALLY IN USE. IN MOST EXPERIMENTS INVOLVING EXCITABLE TISSUE, IT IS THE CURRENT DELIVERED TO THE PREPARATION THAT IS OF IMPORTANCE. EXCITATION THRESHOLDS AND GRADATION OF RESPONSE ARE FREQUENTLY DIRECT FUNCTIONS OF STIMULATING CURRENTS. IT IS

THEREFORE AN ADVANTAGE TO BE ABLE TO CONTROL PRECISELY THE CURRENT DELIVERED TO A PREPARATION. THE CURRENT DELIVERED BY A STIMULATOR IS DIRECTLY RELATED TO ITS VOLTAGE OUTPUT AND TO THE EXTERNAL CIRCUIT RESISTANCE WHICH IS USUALLY MADE UP OF THE TISSUE, ELECTRODE, AND CONTACT RESISTANCES. SOME OR ALL OF THESE RESISTANCES WILL VARY WITH TIME, TEMPERATURE, OR CONTACT PRESSURE, AND TEND TO CAUSE CORRESPONDING CURRENT CHANGES. IN ORDER TO DELIVER A DESIRED CURRENT TO A PREPARATION USING A CONTACT VOLTAGE STIMULATOR, IT BECOMES NECESSARY TO MONITOR THE CURRENT OUTPUT AND CONTINUALLY READJUST THE VOLTAGE TO COMPENSATE FOR THESE CHANGES. THE CONSTANT CURRENT STIMULATOR, WHOSE OUTPUT IS INDEPENDENT OF EXTERIOR RESISTANCES, ELIMINATES THIS TIME-CONSUMING AND INEXACT PROCEDURE. IT THUS ESTABLISHES STIMULUS THRESHOLDS IN A FAR MORE RELIABLE MANNER.

PART B INCLUDED: NO

Calendar Year 1962

PUBLIC HEALTH SERVICE - NATIONAL INSTITUTES OF HEALTH

DIVISION OF RESEARCH SERVICES

Summary of Branch Activities

1. DRS-9
Serial Number

2. LIBRARY BRANCH
Branch

3. Malcolm S. Ferguson
Acting Branch Chief

Objectives

The primary mission of the Library Branch is to operate an efficient and comprehensive library and biomedical information program. Its literature resources and bibliographic and other services are designed to support the intra- and extramural research programs and administration of the Institutes and Divisions of NIH. In these activities the Branch must be responsive to the specialized and continually changing technical information needs of the investigator and keep in tune with modern and improved techniques for the storage, retrieval, handling, and dissemination of scientific knowledge available in the world's literature.

Programs

The objectives of the Library Branch are implemented through technical and readers services programs that up to the present have operated largely along lines traditional to library practice. Services to the staff of NIH consist of the circulation of literature, the provision of reference and bibliographic assistance, the translation of foreign literature, and a photocopy service. The literature holdings of the Branch are further supplemented, when necessary, by an extensive borrowing of materials from national repositories in the Washington area and from specialized collections located in various parts of the country. In addition to providing these varied services through its own resources of people and literature, and through the interlibrary loan program, the Branch supports and has professional relationships with specialized satellite libraries and reading rooms located in several Institute buildings and in NIH field operations, both here and abroad.

Every existing program of the Branch is directed toward the rendering of assistance to its patrons--the clinician, the laboratory investigator, the nurse, the communications specialist, the technologist, and the administrator. Additional programs are planned that will improve and extend these services. Significant among these will be inquiry into and exploitation of the newer aspects of the bibliographic process, currently known as documentation, that employ unconventional methods of information handling.

Summary of Progress

During the year extensive studies were made of several fundamental library activities and services. These lead to improvements in book procurement, the binding of journals, photocopying, and translation services. With the availability of additional positions in 1962, it was possible to recruit qualified full-time personnel including some experienced librarians, and, in particular, an adequate staff for the circulation services. Book purchasing was increased to the $50,000 level. Selection, acquisition, and cataloging procedures kept pace with the increased book and journal funds. A start was made in weeding the book collection of outdated material. Additional space was provided for the Cataloging Section to unify its activities. The binding operation was relocated in proximity to the journal publications. Appropriate quarters and necessary staff were provided for the newly organized Group Services Unit. All interlibrary loan activities were consolidated in this Unit, which affords an efficient centralized service for borrowing needed material from other libraries and loaning material to them. Contracts for translations were made with several private organizations as a means of eliminating the backlog and gaining experience with contractors to determine where rapid service of high quality may be obtained. Three exhibits on medical subjects were displayed in the library reading area and this innovation attracted a great deal of interest. The satellite library in the Research Facilities Planning Branch (DRS) is in its third year as provider of literature and reference support to members of that program. Two additional satellite libraries were established under competent librarians, in the Mental Health Study Center, Prince Georges County, Maryland, and in the Laboratory of Perinatal Physiology, San Juan, Puerto Rico.

Progress and Accomplishments

LIBRARY SERVICES

Photocopying. Demand for Xerox 914 photocopying as a circulation service continued to mount as the NIH investigators have become aware of the advantages of securing a personal copy of journal articles to file, mark, or cut as they see fit. The number of photocopies increased 105,000 over the total of 600,000 in 1961. Since over 70 percent of the copies contained two pages of print, the amount of literature reproduced during 1962 approximates 1,200,000 pages. It may be noted that last year the National Library of Medicine photocopied 2,244,000 pages of literature for 2,000 libraries here and abroad.

The extent to which photocopying has come to replace journal circulation is reflected in loans, which amounted to 25,000 volumes, a drop of 25 percent below the number charged out in 1961. Moreover, a constantly increasing backlog of requests for photocopies is accumulating. This situation partly results from the fact that investigators are not writing to authors for reprints as much as formerly. In addition, some may be making excessive requests for photocopying service. With the backlog problem in mind, two studies were made of the service during the year.

Based on these studies, it was concluded that a microfilm system with print-out, such as with the Xerox Copyflo equipment, should be tried on a six-month experimental basis as a means of meeting the photocopy requirements of the NIH research staff, as well as the Branch's own extensive needs.

As an adjunct to proposed equipment for printing out from microfilm, the Branch has already acquired a "Filmac 200" reader-printer that produces immediate hard copy from material on 16 mm. and 35 mm. microfilm rolls, and from aperture cards. To further supplement the Branch's microform equipment, microcard readers and printers are now being examined with a view to purchase, so that the many reports on microcards in the Branch files will be more readily usable.

Interlibrary Loan. All interlibrary loan activities have been consolidated in the Group Services Unit created at the end of 1961. Procedures have been streamlined and improved. There is now a centralized service for borrowing from other libraries the materials needed for NIH investigators and for loaning materials to outside institutions. In 1961, about 10,000 volumes volumes were borrowed by NIH and 1,000 volumes loaned to other libraries. During 1962, more than 12,000 volumes were borrowed and almost 2,000 volumes loaned, indicating that the demand for this service is steadily increasing. Procedures were initiated whereby literature requested by investigators that is in scope for the Library is purchased rather than borrowed. Since it is difficult to borrow current volumes from outside libraries, this material was formerly not obtained for the NIH investigator.

A factor that increases the amount of literature borrowed from other libraries is the loss of volumes and periodical issues from the Branch's own collections due to the lack of security in the library area. (This problem is discussed below.)

Orientation. Although the function of orienting NIH personnel and visitors in the resources and use of the Library has been formally assigned to the Group Services Unit, the program has not been entirely a single organizational responsibility. During the year, Group Services gave 61 separate general orientations to 537 individuals in groups of from three to 30 persons. The reference librarians gave 600 individual orientations that were related more to methods of literature searching, special reference tools, and specific information problems.

Reference. This aspect of Branch service has received continuing but not increased support during 1962. This was intentional since supplementary services--acquisition, cataloging, circulation, etc.--must be operating in an efficient fashion before reference librarians have adequate literature resources and support to provide a first-class bibliographic and information service. Vacancies developing through resignations of personnel in the Reference Section have been filled with professional librarians and a chemist. Recently, a librarian with biological training returned to the Section after serving for over two years in other programs of the Branch.

Over fifty bibliographies and guides of varying lengths were prepared on a wide range of subjects. Emphasis on ready reference has been continued,

with bibliographic compilations having a lower priority. Upon reorganization of the Branch in 1963, a truly responsive, positive, and adequate ready reference service must be developed. Bibliographic and the more specialized types of literature intelligence in the future will have to be carefully considered and defined--and this in relationship to unconventional information handling procedures that may be instituted as a result of inquiry into the newer documentation methods.

An innovation is being tried in the reference service whereby a librarian with appropriate scientific background has been designated as liaison representative from the Branch with the National Institute of Allergy and Infectious Diseases. It is hoped that by having a focal point in the Library Branch for literature inquiries, this Institute can enjoy enhanced library support. If successful with one Institute, this relationship will be extended to other segments of NIH.

Translating. In April, the Translating Section was relocated in divided quarters on the 11th floor of the Clinical Center. However, completely contiguous and reorganized space will be made available to the Section in the near future. Contracts for translations from foreign languages into English were made with three private organizations in addition to U. S. Joint Publications Research Service whose services have been used for three years. These are: Midwest Research Institute of Kansas City, Missouri; Excerpta Medica Foundation of New York and Amsterdam; and Robert E. Asnis of Philadelphia. In this way the translating backlog was reduced substantially. In addition, experience was gained with contractors and knowledge acquired as to which organizations provide rapid translating service of quality.

Two monographs, both Russian, were completely translated into English upon request of one of the Institutes. This form of publication will not routinely be accepted for translating in the future. A considerable number of papers were translated from English into foreign languages for presentation at conferences abroad.

A survey of the translating program was made toward the end of the year by an NIH management intern. Under study were such things as feasibility and cost of microfilming the extensive file of translations for subsequent printout on the "Filmac 300" reader-printer or other printing equipment, translation lending activities, performance standards for translators and the relative cost of translations from contractors as compared with those prepared by Library personnel. A report on this study will become available in January 1963. Already there are indications that certain procedures of operation require modification and that new policies must be determined relative to the services to be rendered in the translating program.

BOOK AND JOURNAL ACQUISITION

Procurement. The report on a comprehensive study by a management analyst of book and periodical procurement at NIH became available early in 1962. The report revealed that library acquisitions account for only a little over one-third of the total expenditures at NIH for literature. The remainder

of the literature materials are purchased for a large number of laboratories, clinics, etc., through regular Institute procurement channels. Since the Library Branch has the reference materials and trained personnel for carrying out its acquisitions program, and has been preparing its own purchase orders for some time, it has enjoyed certain advantages over other units that order books and journals, particularly with regard to the time lag in obtaining the desired material. From the procurement study it was apparent that consideration should be given to the centralization in the Library Branch of all NIH literature acquisition under a system based on mechanized procedures and the use of blanket purchase orders. A decision regarding this was deferred until the Branch is reorganized and more adequately staffed.

Five of the fourteen recommendations in the study have already been effected, involving further delegation of responsibility to the Library Branch so that now it can originate, sign and mail purchase orders for books, journals, and binding. There is now direct communication with vendors and contractors regarding procurement and followup on orders. These changes have greatly expedited the acquisitions program.

Books. During 1962, funds for the purchase of books increased $10,000 over 1961 and almost reached the $50,000 minimum level recommended for this purpose in the 1961 report, "A Medical Intelligence Program for the National Institutes of Health" by Dr. Ralph R. Shaw, School of Library Service, Rutgers University. Approximately 4,300 volumes were purchased and an additional 700 volumes were received as gifts.

Journals. Subscriptions obligating about $40,000 were placed for 1,582 journal titles, with duplicate orders for 207 titles. More than 900 additional titles were received either as gifts or in exchange for Public Health Reports or the Journal of the National Cancer Institute. This makes a total of 2,519 journal titles currently received, an increase of 200 over 1961.

Satellite Purchasing. In addition to the above procurement, books and journals for the three satellite libraries were acquired by the Branch at a cost of $19,000 through obligation of funds from the respective administrative offices for these libraries.

The greatly enlarged literature procurement program of 1962 demonstrates the potential that the Branch has for taking on greater acquisitions responsibility in the future, provided there is an appropriate staff increase in the technical services area.

ORGANIZATION AND VITALIZATION OF THE COLLECTION

Cataloging. After selecting and acquiring library materials the items obtained must be organized through a cataloging program geared to handle the new literature expeditiously, so that it becomes available to the patron in the shortest possible time. While the Branch cataloging staff has been increased somewhat during the past two years, and its working area considerably enlarged, this aspect of technical services still presents

several problems--staffing, procedures, coordination of effort with other library activities--that must be corrected. In spite of these and other problems, the Cataloging Section accomplished much during the year with urgently needed new materials given priority. Cataloging was also performed for the satellite libraries and, where backlogs prevented early handling, the literature acquired for them by the Branch was forwarded to these libraries with a minimum of processing for each item.

Weeding. A critical survey and reorganization of the Branch collection will be carried out during 1963. During the past summer a start toward eliminating out-of-date and seldom used materials was made with the assistance of students. Approximately 5,000 volumes published between 1889 and 1930, together with the 18,000 cards representing them in the public catalog, were retired from the library. Much of the weeded material was forwarded to large repositories in the Washington area--National Bureau of Standards and the National Agricultural Library. It is the intent of the Branch to emphasize current literature in its holdings since the metropolitan area is so rich in library resources. However, the older but still pertinent and used materials will not be sacrificed just to achieve more space and the "modern look".

MAINTENANCE OF THE COLLECTION

Stacks. Several full-time and dependable library assistants were recruited in recent months to maintain the book and journal stacks and this has produced a noticeable improvement in the appearance of these areas. The stack attendants are now able to keep up with the shelving of the large number of volumes used by Institute staff members, or for the photocopying service. With adequate staffing it has been possible to resume reading of the shelves to find and relocate those volumes which are out of place.

Binding. A study documented by photographs was made of the number and type of errors and evidences of poor quality of workmanship found in the journals returned from DeNol Binding Company, the contract binder for the years 1960-1962. This, along with unsatisfactory reports from other DHEW libraries, resulted in the Department's decision to exclude this binder from future consideration. The present contractor, Hertzberg New Method, Inc., is performing more satisfactorily. The binding program was relocated in proximity to the main journal stacks and its quarters are due to be enlarged for more efficient operation. However, problems related to staffing, missing issues, and procedures must be resolved before the binding program achieves its necessary potential.

The output of binding in 1962 dropped below that of 1961 when 5,500 volumes were prepared for shipment. Part of this decrease is due to the fact that fewer summer students were available to assist in the program.

Security. On three occasions in 1962 inventories were taken of books and periodicals in the reference area of the Library, and revealed that over 1,200 volumes were missing without a record of the borrower's identity. It has been found that about 30 percent of the literature missing at any

one inventory reappears on the shelves in 30 days, and that up to 50 percent is returned in six months. Thus, about 90 percent of the volumes unaccounted for are never returned. Similar figures might emerge if inventories were taken of the general periodical and monograph stack areas.

Since the reference and general collections are basic to both the Institute personnel and Library Branch staff for consultation and information purposes, it is essential that non-circulating materials remain on the shelves and that volumes taken from the general collection be signed out.

It has been Branch policy to reorder many important volumes that have been missing for a period of time. In addition, requested missing literature is also obtained through interlibrary loan. Both of these measures are expensive and time consuming, and it would appear that the time has come for radical changes in policy that will ensure greater security for the library holdings. Accordingly, plans have been made for changes early in 1963 that will involve, along with other measures, a checkpoint for patrons as they leave the library and the locking of the library area when no staff members are on duty.

SATELLITE LIBRARIES

In 1960, a reference room, under the supervision of a professional librarian from the staff of the Library Branch, was established in the Research Facilities Planning Branch (RFPB) of the Division of Research Services. For professional guidance this library was related to the Reference Section, Library Branch. Administratively, this librarian was responsible for day-to-day activities to the Chief, RFPB. Early in 1961, it appeared desirable to change the professional relationship from the Reference Section to the Office of the Chief, Library Branch, to ensure that the RFPB Library had the full resources of the Library Branch behind it. Concurrent with this new arrangement, the Library Branch assumed the functions of acquisitions and cataloging for the RFPB library. Such arrangements permit the librarian in RFPB to concentrate on the provision of service to the engineers and technical personnel engaged with problems of laboratory design, building planning and construction, and other such matters related to the research programs of NIH.

The harmonious and profitable relationship that developed in this experiment prompted the Library Branch to promote similar arrangements outside the Division of Research Services during 1962. As a result, two more satellite libraries were set up along essentially the same lines of responsibility and support--one in the Mental Health Study Center, National Institute of Mental Health, located in Prince Georges County, Maryland, and the second in the Laboratory of Perinatal Physiology, National Institute of Neurological Diseases and Blindness, situated in San Juan, Puerto Rico. The literature requirements of these research programs are quite different from that of RFPB due to the nature of their specializations and the emphasis on the behavior of people and the functioning of the human body. The Library Branch has gained valuable experience in providing services to the satellite libraries. These can be improved during 1963, particularly with regard to the carrying out of commitments to catalog all new materials.

The pattern of assistance which has been developed for these specialized reference units can be exploited as other satellite libraries come into being in Institute research programs having need for their own reference collections. If the Library Branch provides optimum service to the satellites in the Institutes and Divisions, and if it provides them with imaginative, positive, and coordinated leadership, the quality of bibliographic intelligence services existing in certain areas of NIH will be greatly improved.

MEETINGS, EXTRAMURAL ACTIVITIES, TRAVEL, AND VISITORS.

Moderate emphasis has been placed on the attendance at library, documentation, and scientific meetings and seminars in the Washington area by the professional staff of the Branch. In June, during the Special Libraries Association Annual Meeting, the Library Branch was host to over 100 visitors. In addition, there are metropolitan chapters of library and information specialty groups at whose meetings the Branch is actively represented. One librarian attended the Annual Meeting of the American Library Association in Miami Beach and another that of the Medical Library Association in Chicago. At the latter meeting, the Chief, Reference Section, served as a discussion leader on Biographical and Directory Information in a Sources of Information seminar.

The Acting Chief, Library Branch, presented a paper on mechanized literature searching at a symposium, "Information Retrieval in Action", sponsored by the Center for Documentation Communication Research of the Western Reserve University School of Library Science. During September, the Acting Chief, Library Branch, visited technical libraries in Delft, Holland and Warsaw, Poland. In addition, publications, library, and language translation problems were discussed with personnel at the home office of the Excerpta Medica Foundation in Amsterdam.

The Assistant Chief, Library Branch, served during the year as an active member of a U. S. Civil Service Commission Bureau of Programs and Standards committee to develop a Civil Service test to be adopted for librarians. The Assistant Chief has also been a member of the Publications Committee for the Second International Congress on Medical Librarianship to be held in Washington in June 1963.

A number of staff members attended courses and seminars useful to their work that were offered in the Washington area, such as courses in the Department of Agriculture Graduate School. During the summer in-service training in Russian was given by a member of the translating staff to several summer students working in the Library.

The Library Branch continues to receive many visitors from here and abroad. In the main, those from abroad were librarians on official visits to this country whose itineraries are prepared by the foreign visitors committees of the American Library Association and the Medical Library Association. Others were foreign librarians holding various fellowships or scholarships. Many have heard about the Branch's active programs in support of biomedical research, and wish to become better acquainted with certain aspects of these operations.

EXHIBITS

An innovation in the Library that has attracted a great deal of attention and favorable comment is the inauguration of exhibits on medical subjects. With the cooperation of the Medical Arts and Photography Branch, DRS, three exhibits were prepared and arranged in display cases: one on Theobald Smith, the noted American microbiologist; one on Nathan Smith, a medical educator; and one depicting 75 years of research on infectious diseases in the Public Health Service, particularly by NIH and the Hygienic Laboratory that preceded it. A continuation of this information and teaching project can do much to enhance the prestige of the library programs in readers services.

STAFFING

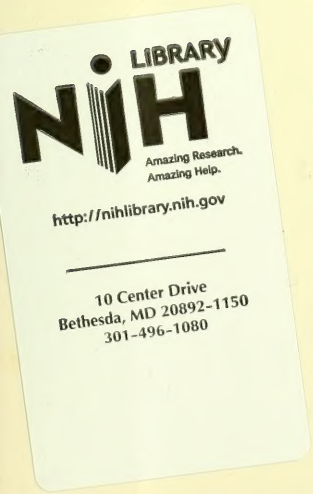
The former Chief of the Library Branch departed in February 1961 and, from then until August 1962, an intensive search was carried on for an experienced and competent librarian to direct the central literature services of NIH. Recruitment culminated in the appointment of Mr. Jess A. Martin, Health Services Librarian of Ohio State University, as Supervisory Librarian, and he will join the Branch on February 1, 1963.

In the absence of a permanent Chief of the Branch, intermediate supervisory positions have been deliberately kept vacant so that these could be filled when the final reorganization of the library is effected. Plans are now underway for regrouping most Branch activities into two Sections--Readers and Technical Services--with permanent supervisors to be appointed. Once this superstructure becomes a reality the various library functions can be properly coordinated and the Branch begin at long last to operate as a more unified and effective organization. The Shaw report that became available in February 1961, has served and will continue to serve as a guide in the development of a highly responsive and comprehensive library service program. Only through the recruitment of a number of additional people of the highest caliber, both as to professional and intellectual capabilities and administrative acumen, and working together with the present staff, will the Library Branch realize its full potential as a biomedical information center.

During the year there were a number of resignations--professional librarians, subject specialists, a translator (retirement), library assistants and clerical personnel. However, in only one instance did a librarian, the Chief of the Circulation Section, leave for advancement. None appear to have resigned because of uncertainty regarding the future or existing working conditions. This is rather remarkable in view of the fact that the Branch has been without permanent leadership for almost two years. Undoubtedly, this record speaks well for NIH as a place of employment. In addition, it suggests that the Library Branch may provide a stimulating and satisfying environment for its people.

Six professional librarians, a chemist, an administrative assistant, three library assistants, a messenger clerk, a mail clerk and three machine operators (photocopy) were recruited for full-time work during the year. While some of these were replacements for individuals who left the Branch,

there was an overall increase in permanent staff of eight employees during 1962. As a result of special and sustained effort the circulation program is now completely staffed. This is stressed because this function is the one that puts literature directly in the hands of the user. Refinements in literature service, such as greater emphasis on bibliographic assistance, must await further staffing. At present, the Branch has sixty-seven full-time and part-time employees. Last summer fifteen students were on full-time duty and served effectively in several of the library programs. There are still several unfilled permanent positions in the Branch which are being held open until the impending reorganization is undertaken.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